THE PATHOLOGY OF PNEUMONIA.*

BY

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DR. GASKELL said that his purpose was to submit the results of certain experiments which had occupied him during the last seven years and had yielded, as he thought, certain facts which could be legitimately applied to man. They showed that the titre of the infecting organism was all-important, and that this determined both whether a lesion would be produced at all and what the nature of that lesion would be. An attack of lobar pneumonia in the healthy adult was due to organisms of titres between 5 and 7, which were otherwise comparatively rare. The deduction might be made that it was spread by direct contact, infection passing from throat to throat, though very possibly intermediate carriers were often concerned.

In any attempt to produce infective lesions by experiment estimation of the virulence of the infecting organism was of the utmost importance; this was particularly so in the case of the pneumococcus, because its virulence varied so greatly. Earlier workers used organisms which answered the criterion that one-millionth of a cubic centimetre of an eighteen hours' broth culture killed mice when injected intraperitoneally; their method of obtaining such a dose was by successive dilutions in broth. This criterion was open to the objection that the few organisms injected lay in a comparatively large volume of a nutrient fluid which was not rapidly absorbed and in which they could multiply freely, the host acting as a living test tube. The method, therefore, did not give an accurate measure of the minimal lethal dose to mice.

The virulence or pathogenic power of an organism depended upon two factors which could not be measured separately—namely, the invading power of the organism and the resisting power of the host. In order to obtain any measure of virulence it was necessary, therefore, to standardize as far as possible one of these factors—namely, host resistance. The measure then used is the smallest dose of the organisms which will cause death. It was, therefore, essential to employ a method which ensured immediate reaction between the attacking organisms and the defences of the body. The organisms must be denied all facilities for multiplying other than those provided by the tissues of the host. The mouse was an experimental animal eminently suitable for the measurement of pneumococcal virulence, owing to its high susceptibility, and if healthy mice whose weight lay within narrow limits were used a fairly satisfactory stabilization of the host factor was obtained. The possibility of vitiation of the measurement of the dose of the organism by multiplication in the fluid introduced could be obviated by dilution in normal saline, which was rapidly absorbed. Such dilutions must, however, be injected immediately, as the pneumococcus rapidly died in saline solution.

His own experiments had been almost entirely carried out with a single strain of pneumococcus whose virulence had been altered at will. For convenience the measure of virulence or titre had been taken as the logarithm of the reciprocal of the minimal lethal dose—that was to say, the titre being x , the minimal dose was $1/10^x$. The actual dose given could be roughly estimated from the fact that an eighteen hours' broth culture contained between 200 and 500 million organisms, or otherwise 2×10^8 to 5×10^8 . The minimal lethal dose at titre 7 therefore lies between 20 and 50 cocci only, and titre 8 becomes an absurdity.

The experimental animal selected was the rabbit, an animal moderately susceptible to the pneumococcus, which fortunately proved very comparable to the human host in its relationship to infection.

Lung Structure.

Dr. Gaskell said:

In the mammalian lung the bronchial tree is lined with ciliated epithelium up to its terminal branches, which end in one or two terminal bronchioles having non-ciliated epithelium,

each of which opens into an alveolar unit consisting of various portions, which have been accurately described by Miller, and named by him, on the analogy of a classical house, the vestibule, the atria, and air vesicles with terminal pouches or air cells. Owing to the absence of ciliation of these terminal bronchioles any material which reaches into or beyond them is not removed, but is speedily sucked in by the respiratory movements and is bound to become spread through the whole system. Such a terminal bronchiole with its air spaces may be termed an alveolar unit, and any infection which reaches it necessarily involves the whole unit.

These terminal units not only occur at the end of terminal branchings, but are also given off throughout the bronchial tree, rising from the largest bronchi, usually being in pairs, and connected to such a bronchus by only a very small ciliated bronchiole. The central part of the lung is composed of such units, which are thus in very intimate connexion with the biggest bronchial tubes.

Owing to the respiratory to-and-fro current aided by the ciliary action of the epithelium, material lying in the large tubes is rapidly side-tracked into these central units. There is a great tendency for these small branchings consisting of a tiny bronchiole with two units attached to occur in whorls of three, a peculiarity of structure which explains the trilobed appearance of the consolidation not infrequently seen in broncho-pneumonic conditions.

Method of Experiment.

Dr. Gaskell then described the method he employed to make certain of introducing pneumococci into the lung itself.

Tracheotomy was performed, and a soft rubber tube of such size as to engage in the opening of the main bronchus to one lobe of the lung passed down the trachea. The culture was injected into the tube by piercing it with a fine injection needle, and the material blown into the lung by means of a puff ball on the external end of the tube. It was found that by far the commonest site of any lesion produced was the lower lobe of the right lung, which is of interest, because of the frequency with which this lobe is the site of pneumonia in man. The probable explanation in both cases lies in the fact that the bronchus of the right lower lobe is in the most direct line with the trachea. As a rule 1 c.cm. at least of the culture was injected, and it was estimated that about half reached the lung itself, the remainder being lost in the tube. Over eighty experiments were performed with the Type I pneumococcus, whose virulence varied from a titre of below 3 to one between 6 and 7. The nature of the lesion obtained depended entirely upon the virulence of the organism used, and not upon the dose given.

Broncho-pneumonia.

When organisms of about titre 4 were introduced into the rabbit's lung, they and the material in which they were contained were speedily side-tracked by the respiratory current and ciliary movement into the nearest alveolar units. Frequently the material had reached only the larger bronchi and had been side-tracked into the central units in connexion with them, thus giving rise to a patchy central pneumonia; if the material had spread more widely a diffuse broncho-pneumonia was produced. The inflammatory reaction which took place remained confined to the units thus invaded, which were often in the earlier stages clearly delineated by the consolidated area. It was only in the early stages that cocci in any quantity could be identified in such a lesion. They appeared to have little power of multiplication and to be rapidly destroyed by the inflammatory reaction, though, as would be mentioned shortly, this destruction was not always complete. Later the neighbouring alveoli began to take part in the inflammatory reaction, so that the unit outline became obscured.

The capillaries of the consolidated patch became more and more engorged, reaching a maximum at about the fourth or fifth day. They then gradually became more inconspicuous, and in the meantime the more fluid exudate became slowly absorbed by local lymphatics.

These experiments threw light on that low grade form of broncho-pneumonia which occurred in children, characterized by the successive appearance of fresh patches of lung infection which might even continue for as long as six months. The explanation they suggested was that the local defensive reaction in the original lesions had not been sufficiently intense completely to destroy the invading cocci.

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Lobular Pneumonia.

As the virulence titre of the invading organism increased, though the initial states of the cleansing of the bronchi and side-tracking of the infecting material were the same, the inflammatory reaction became both more extensive and more intense in nature. The power of the cocci rapidly to reproduce themselves was increased, so that they were much more easily found in the earlier stages, and were no longer confined by the limits of the alveolar unit, but spread directly into others lying around it. The nature of the inflammatory reaction was changed owing to an increase of the numbers of polymorphonuclear leucocytes and consequently a diminution in the preponderance of the larger alveolar cells. The serous exudate was increased and fibrin might begin to be formed in it.

The capillaries again became more and more engorged up to about the fourth day, but then, especially in the centre of the patch, they became rapidly obliterated by the pressure of the exudate in the alveoli. It was during this early period that cocci were most conspicuous. Though the inflammatory patch had become much larger, its periphery was still similar to that of the smaller patch with catarrhal exudate taking place at a fairly early stage. These patches might become so large that they coalesced to form the more extensive lobular type of lesion.

Lobar Pneumonia.

With a further rise of titre to a value of between 5 and 6, if a suitable dose was introduced, a lobar lesion was obtained. The organisms had now a much greater power of reproduction and invasion, and spread rapidly throughout the lobe, being apparently able to keep in advance of the host's attempt to localize them by inflammatory reaction until the periphery of the lobe was reached. A lobar lesion twenty-four hours old showed the process clearly.

In this lobar form of lesion the distension of capillaries did not reach its maximum till about the fourth day, after which the capillaries became somewhat suddenly obliterated by alveolar pressure. The lymphatic system became widely dilated throughout the lobe, distension reaching a maximum at about the third day. The large lymphatics round the larger vessels were then extremely conspicuous, and the bronchi and bronchioles were widely involved; they were filled with exudate and merged into the general consolidation. Cocci were most conspicuous at the spreading edge in the earliest stages. They could easily be found up to the third day, with much more difficulty on the fourth day, and had practically disappeared by the fifth day.

Lymphatic Drainage.

In a few experiments at the lobar titre the involvement of the lymphatic system might cause fatal results. Though the lymphatic channels contained all sorts of debris which must have been derived from the alveoli of the lung, free cocci were, as a rule, completely absent; only an occasional polymorphonuclear cell contained them, and the contrast was great between the wide lymph channel and the alveoli next to it, in which free cocci were numerous. Occasionally an intense invasion of the whole lymphatic system had taken place and the picture was reversed.

These results were perhaps of wider and more general application. They indicated that the swelling of the lymph gland, which belonged to any inflamed tissue, was usually caused by debris drained from the part affected, which was in itself sterile, except for the presence of organisms which, as a rule, were safely enclosed in leucocytes, and became filtered out in the peripheral sinuses of the lymph gland. Such organisms were mostly killed by the leucocytes; if all were destroyed the gland subsided without breaking down, but if some were successful in destroying their host, the gland then suppurated.

Occasionally, however, an infection was of such virulence that the power of resistance of the peripheral lymphatics became destroyed. The lymphatic system draining the part underwent a true invasion and acute lymphangitis occurred.

Invasion of the Blood Stream.

In all experiments where definite lesions had been obtained and the animal had been killed on the first or second day, blood cultures yielded positive results. By the fifth or sixth day, even when the lesion was severe,

the blood culture had almost always been sterile. Thus organisms were always present in the blood at the earlier stages.

Pleurisy.

The relation of pleurisy to lung lesion varied very considerably. An intense form of double pleurisy and pericarditis might occur with titres of high virulence, and probably developed with extreme rapidity, beginning within twenty-four hours of invasion. Pleurisy has also been found with milder types of lesion due to cocci of lower virulence in connexion especially with the lobular type of lesion. In its mildest degree it consisted of a patch situated over a lobular lesion which had just reached the surface; the patch then had been found to be sterile at all stages. When the lung lesion was larger, the pleurisy, though local, was sometimes infected, but usually when this had taken place the whole pleural cavity soon became involved and considerable effusion occurred. A lobar lesion had also been accompanied by unilateral pleurisy with effusion.

Pericarditis.

In a few experiments the pericardium alone became infected, both pleural cavities escaping. The relationship of the root of the lung to the pericardium being very close, an infection mainly localized to the central region of the lung near the root could reach the surface, where it lay against the pericardium and directly invaded this cavity. Such pericarditis, if recovered from, gave rise to adherent pericardium, which suggested that certain cases of this condition might arise from a pneumococcal infection by way of the lung.

Crisis.

On the strength of the facts above described Dr. Gaskell attempted an explanation of the crisis in lobar pneumonia. He said:

I have already stated that cocci have practically disappeared from the lung on the fifth day, but are usually easy to find in the more severe lesions until then. Now the chief toxin of the pneumococcus is an endotoxin which is only liberated when the cocci are killed. There is thus an increasing liberation of endotoxin up to the fifth day, but after that the supply practically ceases. One of the factors determining the crisis may therefore be the final neutralization of endotoxin by the defences of the body forty-eight hours later on the seventh day. Another extremely interesting phenomenon has been demonstrated by Armstrong. He has shown that in lobar pneumonia the protective power of the serum, which is extremely slight at the onset of the disease, practically vanishes after twenty-four hours and remains absent for the first four days. On the fifth day it suddenly reappears and increases enormously and with great rapidity to a maximum on the seventh or eighth day. It then slowly diminishes throughout convalescence. The rapid rise of this power to destroy pneumococci coincides with the crisis. The combination of these two processes thus affords some explanation of the regularity with which crisis occurs on or about the seventh day.

Low Virulence Organisms. Terminal Pneumonia.

No experimental method of lowering the resisting power of the host had been attempted, but Dr. Whittle had been approaching the problem of the nature of terminal bronchopneumonia from the clinical side, and had also attempted to correlate the titre of organisms obtained from human lung lesions with the experiments Dr. Gaskell had described. He had had the opportunity of examining strains from a considerable number of cases of pneumonia, extending over nearly two years, which had occurred in a somewhat isolated village near Cambridge; the outbreak had therefore been of the nature of an epidemic. The titre of the strains recovered had been remarkably constant, and, the number of the inhabitants of this village being comparatively small, it was possible to draw up a scheme of the paths infection had probably taken. In this instance a pneumococcus of high titre had therefore been definitely traced from case to case by actual direct contact. These results opened up the prospects of control of pneumococcal infection in so far as lobar pneumonia in the healthy adult was concerned, and pointed very strongly to the necessity of the isolation of this type of disease. The occurrence of pneumococci of titre 5 or over in the human throat was undoubtedly very uncommon; the organisms with pneumococcal reactions which were present were almost always of quite low titre.