

ON A PLEUROPNEUMONIA-LIKE ORGANISM IN LUNG LESIONS OF RATS, WITH NOTES ON THE CLINICAL AND PATHOLOGICAL FEATURES OF THE UNDERLYING CONDITION

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(With (double) Plate I, containing Figs. 1-22)

IN this Institute a lung disease of the laboratory rat has been well known and recognized as a clinical entity since Petrie & Macalister (1911) and Macalister & Brooks (1914) described the condition among wild rats under examination for plague in Suffolk and Essex. Petrie describes the macroscopic appearance of the lesions as follows: "In the early stages, the lungs were found on incision to contain one or more small cavities, full of glairy, semipurulent material. In advanced stages, the normal lung tissue was replaced almost entirely by a system of large cavities full of thick caseous pus." It would appear that this same condition has been studied recently by Passey *et al.* (1936) in their paper on "Bronchiectasis and metaplasia of the laboratory rat". It has also been the object of bacteriological investigation. Ordinary microscopical and cultural methods, however, have so far yielded no definite information with regard to a possible causative agent. Consistent isolation of a particular organism has never been obtained though some interesting findings have been published. Meyer (1928) supplies a useful résumé of these reported findings in rat "pneumonia" together with some notes of his own observations.

Tunncliffe (1916) examined "sixty white rats showing acute or chronic bronchopneumonia". She observed "a long, fine, straight or wavy filamentous organism" in smears or by darkground illumination in 56 out of 60 cases, which stained "fairly distinctly" with Giemsa stain and carbolfuchsin-violet. She was able to distinguish it from cilia by its greater length, more pointed ends, and its occasional wavy forms. She could demonstrate it in the tissues by Levaditi's method. The cultural results did not correspond with these findings. From the lesions of thirty-three rats growth could not be obtained; in some cases a variety of insignificant bacteria were cultured; on twenty occasions a special, Gram-negative organism, showing swellings of irregular shape, was obtained which Tunncliffe classed among the Streptothricaceae. She emphasized that successful cultures of this organism were more frequent in severe cases of disease and in lesions where other bacteria were present than in those cases which represented a less advanced condition.

Jones (1922), who also undertook a bacteriological investigation of pneumonia in rats, found in eleven cases organisms closely resembling Theobald Smith's *B. actinoides* which he designated as *B. actinoides muris*. The morphology of both varieties found respectively in bronchopneumonia of calves (Th. Smith) and of rats (Jones) is characterized by the presence of bacillary and large club-shaped forms. It is to be noted that Jones only occasionally isolated *B. actinoides muris* from the lung lesions of rats and that "in many instances growth could not be obtained".

In agreement with Jones's studies are the findings of Nelson (1930-32). He isolated *B. actinoides muris* in 35 per cent of his cases from the lung lesions of albino rats but in 42 per cent there occurred no growth at all. Nelson's statements concerning the coincidence of middle ear infection and pneumonia in tame and wild rats are of interest from the fact that this middle ear condition yielded on cultivation a wide variety of microbes and *B. actinoides muris* was frequently isolated.

When one reviews the records in the literature, some points of interest present themselves. Though the condition of the lungs seems to have been characteristic, it was not possible to culture one and the same organism from all or most of the cases. From a great number of cases no growth at all was obtained. Tunncliffe cultured a so-called *Streptothrix* and Jones & Nelson *B. actinoides muris* from about one-third of their cases, results which seem to be more than mere accidents.

DESCRIPTION OF THE NEW BACTERIOLOGICAL FINDINGS (E. KLIENEBERGER)

My attention was drawn to the "bronchopneumonia of rats" because in a search for *Streptobacillus moniliformis* in the nasopharynx of rats I found that "pneumonia rats" were more frequently carriers of this organism than rats with lungs of more or less normal appearance.¹ It had been shown in previous investigations that the *Str. moniliformis* is a symbiotic culture containing two organisms, a streptobacillus and a pleuropneumonia-like microbe which was designated L_1 (Klieneberger, 1935, 1936). In the course of the investigations on "pneumonia rats" material was transferred from lung lesions to plates of the special medium which is favourable for the growth of the pure L_1 organism (Klieneberger, 1936). After 2-4 days of incubation I observed by microscopical examination tiny colonies covering the plates in large numbers. They were characterized by a darker centre and a ring zone scarcely different in colour from the medium (Pl. I, Fig. 1). Usually these colonies had grown up as pure cultures in their thousands; sometimes they came up in masses between larger colonies of bacteria of different kinds. It was easy to obtain a pure subculture on the same medium if material was transferred abundantly. This was achieved by cutting out a small piece of the grown medium with a strong

¹ Strangeways (1933) was able to demonstrate the *Str. moniliformis* in the nasopharynx of 50 per cent of all tame and wild rats examined without reference to the condition of their lungs.

platinum loop and by moving its grown surface over a new plate. The pure cultures so obtained grew well in passages on the special medium if subcultured every third day. They resembled on solid media the L_1 growth with the only difference that the old L_1 strains—separated from *Str. moniliformis* cultures—were growing now in larger colonies and showing a coarser surface-structure than the new strains obtained from rats' lungs (Figs. 1, 2). In liquid medium the rat strains still grow very slowly; they form tiny colony clumps attached to the tube walls, settling down to the bottom in a similar way to the old L_1 strains but very much more delicate. The microscopical examination of the L_1 -like strains from the lung lesions was carried out by four different methods. The ordinary Gram-stained smear did not reveal any definite microbial structures, but only a few tiny granules. The direct agar microscopy, the dark-ground preparation and the agar fixation technique (Klieneberger, 1936) demonstrated the filaments, granules and different globules which characterize the L_1 and other pleuropneumonia-like organisms. The new lung strains are distinguished by a greater delicacy in all their elements if compared with the old L_1 strains (Figs. 1, 2, 3, 5 and figures in previous papers). They may, however, acquire a coarser growth after numerous passages on the same medium.

Table I

No. of rats	Age	Lung condition	Exudate	Bacteria cultivated from lung	L_1 microbe grown	Particulars
6	Newborn	Of normal appearance	—	—	—	—
1	Adult	Of normal appearance	—	—	—	Wild, brown rat
1	1 month	Parts of transparent appearance	—	—	—	Discarded*
1	2 months	Parts of transparent appearance	—	<i>Streptococci</i>	—	Discarded
1	8 months	Of normal appearance, but small black spots on surface	—	—	—	From stock
1	8 months	Two foci	Slimy	—	—	From stock
4	1-2 months	Characteristic lesions	—	—	+	Discarded
1	8 months	Characteristic lesions	—	Gram-negative bacilli	+	From stock
1	2 months	Parts of transparent appearance	—	<i>Streptobacillus moniliformis</i>	+	Discarded, sick, very thin
1	2 months	Characteristic lesions	Gelatinous	—	+	Discarded
5	1-2 months	Characteristic lesions	Glairy	—	+	Discarded
2	8 months	Characteristic lesions	Glairy	—	+	From stock
1	8 months	Characteristic lesions	Glairy	<i>Streptococci</i>	+	From stock
1	2 months	Characteristic lesions	Glairy	<i>Streptobacillus moniliformis</i>	+	Discarded, died
1	2 months	Characteristic lesions	Glairy	<i>Streptococci</i> and Gram-negative bacilli	+	Discarded, died
1	Adult	Two foci	Purulent	—	—	Wild, brown rat

* "Discarded" signifies that the animals became affected in the course of vitamin and endocrine experiments.

Twenty-nine rats were examined in all. Their origin, age, lung condition and the results of the cultural examination on the special medium are given in Table I. From lungs of normal appearance no L_1 culture was obtained. The characteristic lung condition—usually in rats discarded from vitamin or endocrine research experiments—was present nineteen times and yielded an L_1 -like culture in seventeen cases. In twelve cases hardly any other organisms developed on the plates, while in five cases various bacteria grew up in

addition (streptococci on three occasions, *Str. moniliformis* on two); in these five cases the L_1 colonies preponderated. The *Str. moniliformis* cases were specially severe cases of disease.¹ Direct microscopical examination of lung lesions was carried out by the dark-ground method (Fig. 6) and stained smears or impressions (Figs. 4, 7–18). The preparations—especially those from the exudate—revealed in the main two kinds of elements, so far not found in lungs of normal appearance, viz.: (1) long, sometimes wavy and branched filaments showing in the living state a peculiar kind of flexibility which may be active to a certain degree, and (2) globules of different size and shape, free and fixed to filaments. Information could always be obtained from the dark-ground preparation, but the stained film was only occasionally successful in showing up clearly the pleuropneumonia-like structures.

NOTES ON CLINICAL AND PATHOLOGICAL FEATURES IN AFFECTED ANIMALS
AND ON THE BACTERIOLOGICAL FINDINGS BY ORDINARY METHODS
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The histological appearance of the lungs of these rats varies within very wide limits, but may be said to present distinguishable stages of a progressive pathological condition. There are usually extensive changes in the structure of the lung before any radical macroscopic alteration can be seen, and it is difficult to judge from a naked-eye examination in the early stages whether a rat is, or is not, infected. Sometimes the pleural surface shows small petechial haemorrhages, sometimes it is covered with darkish, pin-point gelatinous spots, but the major bronchiectatic lesions are developed in those areas of the lung which are probably least expanded in ordinary use; these are fairly regular in their distribution, and in the order in which they occur. The small lobe is usually the first to present the characteristic change, i.e. to become a mass of grey translucent nodules; then follow the apices of both the upper lobes, and later the lowest part of the lower lobes. The right side appears usually to be affected before the left. Sometimes all the lobes of one lung are macroscopically normal, while the other is so changed that it seems very unlikely that it can still be functioning; indeed, the chief symptom of the more advanced condition is the way in which the rat breathes. Instead of the rapid and shallow breathing of more normal animals, the movement of the flanks in the later stages is deep and laboured, though the rats do not seem to suffer any impairment of appetite or ordinary movement while they are under observation, a period covering, at its longest, about 18 months.

Source of rats examined

Most of the rats examined for the purposes of this investigation were discarded (*a*) from the breeding room, or (*b*) from some experiment in the Institute, either because they had “snuffles”, which is suspected to be a

¹ Before these investigations were commenced *Str. moniliformis* had already been isolated in a few cases from heavily infected rat lungs.

preliminary stage of the disease, or because they showed the typical breathing of the advanced stage. It is to be noted that there are no obvious symptoms by which to recognize the intermediate stages. In most of the rats examined, the lung changes had not reached the point at which the gelatinous nodules are replaced by a caseous pus, but some few animals were seen in which one or more of the lobes were merely cavities filled with thick dry pus. These abscesses were never seen in animals from the breeding room, and only occasionally in those from the experimental rooms. The infection is essentially of the chronic type, and probably the rats are drafted out of the stock room before they have reached this stage. Stock rats are kept for rather less than a year for breeding purposes, but since the caseous stage is reached in experimental rats less than 2 years old, it is not unlikely that experimental conditions accelerate the course of the disease. In this connexion it must be remembered that Petrie described similar lesions in the lungs of wild rats examined for plague, so that though the disease may be aggravated, it is not engendered by the conditions under which a laboratory rat lives. At the same time, it is justifiable to say, at least, that every rat in the stock discussed here is predisposed to this infection; this seems less sweeping than to say that every rat is infected from birth, but it is nevertheless rare to find lungs normal in outward appearance, and it is rarer still to find normal lung tissue on histological examination. There is certainly a difference in the age at which the major changes develop; some animals may have severe lesions when less than 2 months old, even though they have been kept always at a constant temperature and fed on a generous diet; other—and experimental—rats have lesions no more severe at 8 months old. If, through a sudden change in the weather, or by some fault in the heating apparatus, the temperature of the room in which the rats are kept drops appreciably, they may contract a true pneumonia. This is readily differentiated from the lung disease under discussion since (*a*) the pneumonia is acute and rapidly fatal, while the bronchiectasis characteristic of this disease is chronic and never fatal within the ordinary span of the life of a laboratory rat; (*b*) the affected parts of the lung are grey and translucent, or sometimes haemorrhagic, but do not show the grey nodular distensions of the chronic conditions; (*c*) the histological picture is typical of a clinical pneumonia in which the alveoli are filled with fibrin and cells, whereas the chronic condition is a bronchiectasis with its accompanying atelectasis; (*d*) a heavy streptococcal infection is usually found on bacteriological examination, whereas, in the chronic condition, the tissues are, when tested by ordinary methods, often completely sterile. Though bacteriological investigation on ordinary lines does not seem to yield much relevant information if the bronchiectasis is uncomplicated by an obvious secondary infection, the histological findings suggest that its primary cause lies in some source of stimulation detrimental to the bronchial epithelium, and that the progress of the condition is a more or less mechanical result of continued irritation. The long course of the disease precludes the likelihood of toxic action, and, until the structure of the lung

tissue becomes completely disorganized owing to the accumulation of the grey glairy mucus, only the bronchial tissue shows marked change. The ultimate stage in which a whole lobe is reduced to a caseating mass records the final defeat of the mechanisms of defence. The sequence in which these mechanisms are employed is tolerably easy to follow. First, a greater secretion on the part of the epithelium of the bronchioles results in the presence of a small quantity of mucus in the lumen (Figs. 19, 20). This secretion actively increases and the columnar cells of the epithelium begin to proliferate. A severe peribronchial lymphocytic infiltration takes place at the same time (Fig. 21). Later, the bronchioles become distended with accumulation of mucus, and the surrounding alveoli are correspondingly atelectatic, partly owing to the mechanical pressure of the enlarging bronchioles, and partly to the failure of the air supply. Leucocytes begin to immigrate into the lumen through the epithelium, in such numbers, and at such a rate, first mononuclear, and later polymorphonuclear cells, that the epithelium seems to be pushed from its base, and forms projecting papillae not unlike the smaller fimbriae of the Fallopian tubes, except that in sections of these lungs the regular palisading of a normal ciliated epithelium is never seen. The individual cells lie jumbled together and at all angles, so that it is difficult to distinguish between the true epithelium and the invading cells, while the cilia either lie matted together or are desquamated. Even allowing for the contraction of the elastic fibres beneath the basement membrane, the vacuolation, fimbriation and proliferation of the ciliated cells are prominent features. Eventually the bronchioles are completely occluded by polymorphonuclear cells, which, like the other defensive agents, are unable to deal adequately either with the original infection or with the damage resulting from its presence (Fig. 22). Finally the bronchial epithelium is destroyed, the polymorphonuclear cells, in their turn, die, and all that is left of the affected lobe is a mass of necrotic pus cells surrounded by fibrous tissue.

Bacteriological findings by ordinary methods

The material under investigation for the L_1 organism has also been examined concurrently for the presence of other bacteria. No organism of known pathogenic significance has been found, except where the presence of a true pneumonia was to be suspected, and, as has been said, in the majority of such cases a streptococcus was present in large numbers. The original intention of an earlier investigation into the nature of this rat disease was to try to find some organism of coccal nature specific to the rat bronchiectasis, like that associated with the pneumonia of guinea-pigs, but the typical lesions were so often apparently sterile that the idea was abandoned. Cocci and diphtheroids were sometimes found, as might be expected, especially if small localized abscesses were present. When peptic blood was used as a medium, however, a *pasteurella*-like organism was found to be very frequently present.

This organism is a minute non-motile Gram-negative bacillus, staining intensely with carbol-fuchsin; it produces acid in glucose and saccharose, and occasionally in mannite,

but has no action on lactose or dulcitate; litmus milk becomes slightly acid and indole is produced; it does not grow on gelatin at room temperature, but will do so at 37° C.; it will grow on ordinary agar, but dies out in a few days; it will survive for 3 or 4 weeks at 0° C. after 24 hours' incubation in peptic blood broth at 37° C.; the colonies are smooth round, raised, regular and translucent.

This organism was almost ubiquitous in the rats examined and was even found in the lungs of two rats only 1 day old, but it was not associated with obvious pathogenic action in any of the rats concerned. Since, however, all the rats appear to suffer from a pathological condition of the lungs, and since the bacillus is so constant a finding, it cannot be said with certainty that the presence of the organism has no bearing on the condition. It is not by itself pathogenic, for no experimental infection could be induced in rats, guinea-pigs or mice by its agency.

The rats at one stage suffer from "snuffles", usually a clear, watery, but not copious nasal discharge; sometimes this discharge is slightly blood-stained, and the bacillus is then invariably present. To obtain a culture, the animal's nose was sponged with sterile saline, and then an ordinary nasal swab was held against each nostril in turn. The swab was then plated on peptic blood agar, and the plate examined for the characteristic colonies. Of eighty-two nasal swabs examined, sixty-five yielded a culture of the organism. Sometimes it was present in large numbers, sometimes only one or two colonies were found among cocci, diphtheroids, *B. proteus* and other organisms; when the "snuffles" was marked, the plates showed an almost pure culture in considerable numbers. It was isolated in fifty-seven out of seventy-two cases from the lung tissue; in this it was always very scanty and was never seen in smears from the lung tissue, or in sections. In twenty-eight out of forty-nine examinations, it was isolated from both nose and lung.

Large subcutaneous doses of this pasteurella could be given to rats without serious effect. A temporary general infection was caused, and 11 days after the inoculation the organism could be isolated from the site of injection, lung, liver, spleen and intestinal lymph glands, but 4 months later it had disappeared (except from the lungs) from the other rats in the same experiment. The "snuffles" from which these animals suffer and from which the pasteurella-like organism above described was isolated, corresponds most probably with the "rhinitis" noted by Meyer (1928) and which, he says, "regularly precedes the disease". Unlike those pasteurella organisms which are responsible for rat septicaemia and are highly pathogenic, this strain from snuffles does not appear to be pathogenic *per se*; its interest lies in its presence in almost pure culture in the nose during the "snuffles" stage, though there is no evidence to show that it is directly associated with the bronchiectasis and no proof that the rhinitis is actually a stage of the disease.

DISCUSSION

From the lung lesions of rats a pleuropneumonia-like organism¹ has been cultivated, closely resembling the L_1 microbe. The L_1 organism has been described in previous publications (Klieneberger, 1935, 1936) as the symbiont of a bacillus occurring in all cultures of *Streptobacillus moniliformis*. The source of the strains examined was in most cases the nasopharynx of rats. According to Strangeways's findings it is present in the nasopharynx of 50 per cent of all rats; the new investigations show that it is more frequent in the nasopharynx of rats with lung lesions than in others. Thus the interesting fact is revealed of the presence of *Str. moniliformis* (L_1 plus *Streptobacillus*) in the nasopharynx and the independent presence of the L_1 microbe in the lung lesions of the same animals. In a number of severe cases the *Str. moniliformis* has been found in the lung lesions in addition to the L_1 which, however, preponderated. The etiology of the lung disease cannot yet be fully explained, but there seems to be a connexion between the occurrence of the symbiotic culture in the nasopharynx and the L_1 symbiont in the lung lesions. The occasional presence of the symbiotic culture in the lesions also, may be explained as a secondary invasion. These findings are in agreement with those already recorded in the literature and throw a new light on the results of previous authors.

No previous investigators have succeeded in cultivating the L_1 organism from the lung lesions because they were not in possession of a suitable medium. Tunncliffe, however, as has been said, has already demonstrated microscopically the presence of filamentous formations in fifty-six out of sixty cases of rats' "bronchopneumonia". These were undoubtedly the elements of the L_1 organism now described in these lesions. The *Streptothrix*-like strains which she cultivated from twenty severe cases and in which she also found filamentous structures must have been—according to her description, her illustrations and the present findings—cultures of *Str. moniliformis*.

Jones (1922) and Nelson (1930 *et seq.*) also, it would appear, were dealing with the same organism. Theobald Smith's *B. actinoides*, of calf origin,² must also have been a symbiotic culture closely simulating *Streptobacillus moniliformis*. This is apparent from his detailed descriptions, illustrated by excellent photographs in his papers of 1918, 1921, 1921*a*. It is further very likely that the organism isolated in 1914 by Schottmüller and in 1916 by Blake from two human cases of so-called "rat-bite fever" was nothing other than *Str. moniliformis*. The infections corresponded apparently to those human *Str. moniliformis* infections described by Levaditi, Parker and Hudson, and

¹ Shoetensack described in his interesting papers (1934, 1936, 1936*a*) two types of pleuropneumonia-like organisms which he cultivated from the lungs (and other organs) of dogs infected with canine distemper.

² Unfortunately the old strains of Tunncliffe, Th. Smith, Jones & Nelson are no longer available so that comparison is not possible.

others. It is not unlikely that the bite of a rat containing the *Str. moniliformis* in its nasopharynx may cause an infection in man, just as the well-known mouse arthritis (Levaditi, Mackie) is transmissible, as Strangeways first pointed out, from rats to the smaller rodents.

SUMMARY

1. A pleuropneumonia-like organism resembling L_1 in all characteristic features has been isolated from a well-known lung condition of rats of hitherto obscure etiology in seventeen out of nineteen cases.

2. Morphological elements which presumably initiate growth in culture have been demonstrated microscopically in the lesions.

3. *Streptobacillus moniliformis* (i.e. L_1 plus *Streptobacillus*) is a frequent inhabitant of the nasopharynx of rats with lung lesions; it may secondarily invade the lungs as it is found in severe cases together with the L_1 organism.

4. An account is presented of the clinical and pathological features of the underlying condition with which the newly discovered bacteriological findings are associated.

5. The precise role played by the L_1 organism in the pathogenesis of the lung lesions in rats has still to be established and further experiments with this end in view are in progress.

Note. A very brief description of these new findings appeared in *Abstracts of Communications, 2nd Internat. Congr. for Microbiol.* London, 1936.

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EXPLANATION OF PLATE I

- Fig. 1. Colonies of the L_1 -like microbe isolated from the lung lesions of a rat; incubation, 4 days; $\times 30$.
 Fig. 2. Colonies of the L_1 -like microbe isolated from *Streptobacillus moniliformis* (passage 202); incubation, 4 days; $\times 30$.
 Fig. 3. One 2 days old colony of L_1 -like microbe from the lung lesions of a rat. Agar fixation method; fixative, Flemming's weak formula; stain, Giemsa; $\times 900$.
 Fig. 4. Smear from glairy exudate from lung lesions with numerous filaments. Fixative, Wroblewski's; stain, Giemsa; $\times 900$.
 Fig. 5. Colony clump of the L_1 -like microbe from the lung lesions grown for 5 days in liquid medium, consisting of small globules. Dark-ground illumination method; $\times 900$.
 Fig. 6. Piece of tissue from lung lesions showing a number of characteristic filaments attached to cells. Dark-ground illumination method; $\times 900$.
 Figs. 7-18. Photomicrographs of further preparations made directly from lung lesions. Fixative, Wroblewski's; stain, Giemsa.
 Fig. 7. Small filamentous stage of L_1 -like organism.
 Fig. 8. Large filaments; note pear-shaped globule on one of them.
 Fig. 9. Filaments and globules attached to cells.
 Fig. 10. Globules and filamentous network.
 Fig. 11. Branched filaments.
 Fig. 12. Long filaments.
 Fig. 13. Filaments and globules attached to cells.
 Fig. 14. Cell nucleus with globules and filaments in association with it.
 Fig. 15. Globules apparently embedded in the cell protoplasm.
 Fig. 16. Some filaments with globules; note the small globules apparently embedded in the cell protoplasm.
 Fig. 17. Filaments and globules.
 Fig. 18. Filaments attached to cells; one characteristically-shaped globule enclosing a cell.
 Fig. 19. Commencing aggregation of lymphocytes. No obvious lesions in external surface of lung.
 Fig. 20. Increasing aggregation of lymphocytes, vacuolation of epithelium, cells in lumen. No obvious lesions in external surface of lung.
 Fig. 21. Polymorphonuclear cells in lumen, destruction of epithelium, breakdown of wall of bronchiole, severe peribronchial infiltration, atelectasis, commencing abscess. This lobe consisted entirely, on the pleural surface, of slightly raised nodules containing glairy fluid.
 Fig. 22. Vacuolation of epithelium, lymphocytic infiltration, alveoli not affected. This lobe showed isolated nodules containing glairy fluid.

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