HISTOPATHOLOGY OF EXPERIMENTAL INFLUENZA PNEUMONIA

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INTRODUCTION

Since the pandemic of 1918, there have been many investigations of experimental influenza pneumonia. Andrewes, Laidlaw and Smith (1934) (1) have shown that by the technique of intranasal inoculation pneumonic lesion can be produced in mice by influenza virus. Thereafter, a considerable number of investigators have attempted this method. Death of the infected mice and consolidation of their lungs were observed as criteria of effects induced by influenza virus but histopathological changes of their lungs were not sufficiently considered by them.

It was noted by some of these investigators that the occurrence of various bacteria was frequently unavoidable in the lungs of mice inoculated intranasally with influenza virus alone. Hoyle (1935) (2) discovered a small number of gram-negative coccobacilli in all pulmonary lesions produced in mice by intranasal inoculation with influenza virus (W. S.) Straub (1937) (3) was hampered very much by non-specific pneumonia caused partly by viridans-like streptococcus partly by a hemophilus from time to time during his experiment using influenza virus intranasally to mice.

Andrewes, Laidlaw and Smith (1934) also found various bacteria in many affected lungs of mice inoculated intranasally with influenza virus alone but regarded them as of no aetiological significance. Although, Hoyle (1935) stated in his publication that this was not always justified and the presence of bacteria in the lesions often increased their severity. Furthermore, considerable loss of potency was found by many other investigators, for instance Kojima and others (1945) (4), when they attempted to eliminate the organisms by filtration.

In the pandemic of 1890 and 1918, it was recorded by some excellent pathologists, Klebs (1890) (5), Leichtenstern (1890) (6), Abrahams, Hallows and French (1919) (7), Goodpasture (1919) (8), Yamagiwa (1919) (9), and Fujinami (1919) (10), that conspicuous changes of alveolar walls were found in human lungs of influenza pneumonia and they were also observable in non-affected parts of the lungs with pneumatic lesions and in the lungs of patients whose death occurred early after contracting this disease. I think, this fact may be very important and interesting but it attracts no general attention at present time. In general, histopathological changes of human lungs of serious influenza pneumonia look very complicated but one may be allowed to say that wide spread confluent bronchopneumonia is found together with the conspicuous changes of alveolar walls and it is accompanied almost always by marked hemorr-
hage and frequently by suppurative changes of edema. Marked bronchitis and inflammatory changes of interstitium are also frequently demonstrable in it. These changes observed in influenza pneumonia in man may serve as a useful reference to histopathological investigation of experimental influenza pneumonia.

It is believed generally that the cause of influenza is a filtrable virus but a secondary invasion of some bacteria plays an important role in causing influenza pneumonia. I propose to give here an account of the results of my microscopical investigations during experiments carried out in Medical Faculty of Okayama with human influenza virus and some bacteria.

EXPERIMENTAL MATERIALS

Glycerolated human influenza virus strains*, W. S., P. R. 8, Alaska and Onishi, were prepared for this work. Mouse lungs infected with these strains were ground with sand in sterile physiologic sodium chloride solution and the centrifugated suspension was used.

In double infection with virus and bacteria, pneumococcus type I, staphylococcus albus, streptococcus hemolyticus and Mouse Origin Bacteria containing gram-negative coccobacillus were used.

Animals used were healthy mice weighing about ten grams.

Experiment I. Intravenous inoculation

Six mice were injected with 0.025 cc of five percent virus suspension into tail vein and killed with ether on the fourth or fifth day after infection. The lungs of all these mice revealed conspicuous changes of alveolar walls. Alveolar epithelium became large and round and increased in number and sometimes alveolar walls were infiltrated with a few leucocytes. Therefore, alveolar walls became thick and winding. Alveolar epithelium showed frequently foamy protoplasm and sometimes contained vacuoles in it. It's nucleus also became large and light and showed it's structure distinctly, with nucleolus in the centre of it. These changes of alveolar walls (interalveolitis) were found diffusely but alveolar spaces were always empty. Bronchi showed normal state and no remarkable change was found in the perivascular and peribronchial interstitium. Outline of the results are given in Table 1.

For control experiment, four mice were injected into tailvein with 0.025 cc of five percent suspension prepared by grinding healthy mouse lung with sand in physiologic sodium chloride solution and killed with ether on the fourth or fifth day after injection. No case has presented more than slightly reactive hypertrophy of alveolar epithelium.

* All these strains were kindly supplied by Dr. Saburo Kojima, vice-Director, The National Institute of Health of Japan.
Experiment II. Intraperitoneal inoculation

Sixteen mice were injected with 0.5 cc of two percent virus suspension into peritoneal cavity and killed with ether on the fourth to sixth day after infection. Pulmonary lesions observed in this experiment were not essentially different from those in Experiment I. Conspicuous changes of alveolar walls (interalveolitis) described above were found in all these infected mice but the other parts of their lungs were well preserved. Outline of the results are shown in Table 1.

Control experiment using healthy mouse lung showed nothing remarkable beyond slightly reactive hypertrophy of alveolar epithelium.

Experiment III. Intranasal inoculation

Thirty mice were anaesthetized with ether and 0.05 cc of ten percent virus suspension was instillated into nostrils of these mice. Some of them died a few days after infection. When the other mice survived long enough during observation they were killed with ether on the fourth to seventh day after infection. Microscopical changes of these mice lungs were more complicated than those in Experiments I and II. On the whole, congestion was marked, capillaries of alveolar walls were dilated and, here and there, blood escaped not only into alveoli but also into lumen of bronchioles and

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Inoculation</th>
<th>Number of Cases</th>
<th>Bronchitis</th>
<th>Inflammatory changes of interstitium</th>
<th>Interalveolitis</th>
<th>Intra-alveolitis</th>
<th>Hemorrhage</th>
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<tr>
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<td>W. S.</td>
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<td>W. S.</td>
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<tr>
<td>II</td>
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<td>Alaska</td>
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bronchus. In some instances, inflammatory changes of bronchial walls were very marked, bronchial epithelium degenerated and moved towards the lumen of the bronchus and peribronchial interstitium was infiltrated with many leucocytes. An analogous change was also demonstrable in some bronchiolar and terminal bronchiolar walls. Leucocytar infiltration was also found in perivascular interstitium and sometimes perivascular lymphangitis was particularly marked. The interalveolitis described above was always found and alveolar spaces were generally empty but in some instances they contained desquamating alveolar epithelia, red and white blood corpuscles and exsudate. This change (intraalveolitis) occurred first in the area around the bronchus showing marked damage, so it may be catarrhal pneumonia. Sometimes the contents of alveoli were composed mainly of leucocytes (leucocytar intraalveolitis). The results are briefly recorded in Table 1. Cultures from the lungs showing catarrhal pneumonia (leucocytar intraalveolitis) yielded in many cases fair growth of gram-negative coccobacillus on plain agar.

Control experiments were done in order to demonstrate that these changes of mouse lungs are not produced by an aspiration of banal fluid. Of three mice inoculated intranasally under ether anaesthesia with sterile physiologic sodium chloride solution showed no lung lesion except slight cell-crowding in interstitium and hemorrhage. In a similar experiment in which five mice were inoculated with suspension of healthy mouse lung only a slight reaction of alveolar epithelium was found.

Experiment IV. Serial nasal passages

Two to four mice were inoculated intranasally under ether anaesthesia with influenza virus and killed with ether on the fourth to seventh day after infection and more mice were inoculated with suspension of their lungs by the same manner and so on. The interalveolitis described above was transferred from mice to mice constantly. From time to time during this experiment, bronchitis and inflammatory changes of interstitium were found, intraalveolitis (catarrhal pneumonia) was demonstrated in some cases of the third or later generation and hemorrhage was frequently found in greater or less degree. But these changes were not observed constantly.

Experiment V.

Examination day by day after intranasal inoculation

Twenty mice were inoculated intranasally under ether anaesthesia with influenza virus and four mice each were killed with ether on the second to sixth day, day by day, after infection. The interalveolitis described above was found most conspicuously on the fourth day after infection. In the early time (on the second to third day) bronchitis, inflammatory changes of interstitium and hemorrhage were more marked. While, in the later time (on the fifth to sixth day) the interalveolitis recovered somewhat and intraalveolitis (catarrhal pneumonia) was demonstrated in some instances.
Experiment VI.

Double infection with virus primarily and bacteria secondarily

Thirty-four mice were inoculated with influenza virus intravenously or intraperitoneally under no anaesthesia or intranasally under ether anaesthesia and after two or three days, a suspension of bacteria was instilled into nostrils of these mice secondarily. They looked very ill and most of them died within forty-eight hours after secondary infection of bacteria. Microscopical changes of their lungs are summarized in Table 2. The lungs of all these mice revealed a mixed type of pneumonia. It consisted of the interalveolitis described above and an intraalveolitis (catarrhal pneumonia). In a typical example of them, one part showed the interalveolitis alone, other parts showed intraalveolitis and even in it the interalveolitis was still preserved. Hemorrhage was generally very marked in these instances so that the intraalveolitis showed frequently a type of hemorrhagic catarrhal pneumonia and in some of these instances, an appearance of polymorphonuclear leucocytes in the pneumatic areas was particularly marked so that it showed occasionally a type of suppurative pneumonia (leucocytar intraalveolitis). The severest damage of bronchus was found in the cases of inoculation using virus intranasally primarily and bacteria intranasally secondarily, showing sometimes suppurative bronchitis and sometimes obstructed entirely by desquamating bronchial epithelia, leucocytes and mucus. Inflammatory changes interstitium were in general more marked than in the cases of inoculation with influenza virus alone. Edema was frequently observable with pneumatic lesions.

Experiment VII.

Double infection with virus and bacteria simultaneously

Ten percent virus suspension and two percent suspension of Mouse Origin Bacteria were mixed in same proportion and administered to eight mice intranasally under ether anaesthesia. All these mice died four to forty-eight hours after infection. The microscopical changes of their lungs were approximately identical with those in Experiment VI (see Table 2). But the interalveolitis described above and suppurative changes were less striking in these instances. It was demonstrated in Experiment V that the interalveolitis becomes most remarkable on the fourth day after intranasal inoculation with influenza virus alone. In this experiment, death of the infected mice occurred so early that the interalveolitis in their lungs may not reach the most remarkable form at that time. On the other hand, edema was more marked in these instances, here and there, perivascular lymphspaces were flooded with it. Hemorrhage was very marked with great frequency and in some instances, extensive hemorrhagic area was observed. In a few cases, a large number of coccobacilli were discovered as it's pure culture in alveolar spaces.
Table 2. Outline of histopathological changes of the lungs of mice inoculated doubly with human influenza virus and bacteria.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Virus Strain</th>
<th>Route</th>
<th>Bacteria (in.)</th>
<th>Number of cases</th>
<th>Bronchitis</th>
<th>Inflammatory changes of interstitium</th>
<th>Inter-alveolitis</th>
<th>Intra-alveolitis</th>
<th>Hemorrhage</th>
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<tr>
<td>P.R.8</td>
<td></td>
<td>iv</td>
<td>M. O. B.</td>
<td>4</td>
<td>±</td>
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<td>W. S.</td>
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<td>ip</td>
<td>M. O. B.</td>
<td>4</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>P.R.8</td>
<td></td>
<td></td>
<td>Streptoc. hem.</td>
<td>2</td>
<td>±</td>
<td>+</td>
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<tr>
<td>VI</td>
<td></td>
<td></td>
<td>M. O. B.</td>
<td>6</td>
<td>+</td>
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<td>W. S.</td>
<td></td>
<td>in</td>
<td>Staphyloc. alb.</td>
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<tr>
<td>P.R.8</td>
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<td></td>
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<td></td>
<td>Pneumoc. Type I</td>
<td>3</td>
<td>+</td>
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<td></td>
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<td></td>
<td>Staphyloc. alb.</td>
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<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>VII</td>
<td></td>
<td></td>
<td>M. O. B.</td>
<td>2</td>
<td>±</td>
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Simultaneous intranasal double inoculation:

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Route</th>
<th>Bacteria (in.)</th>
<th>Number of cases</th>
<th>Bronchitis</th>
<th>Inflammatory changes of interstitium</th>
<th>Inter-alveolitis</th>
<th>Intra-alveolitis</th>
<th>Hemorrhage</th>
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<tbody>
<tr>
<td>W. S.</td>
<td></td>
<td>M. O. B.</td>
<td>2</td>
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<tr>
<td>P. R. 8</td>
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<td>M. O. B.</td>
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<td>Alaska</td>
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in...intranasally, iv...intravenously, ip...intraperitoneally, M. O. B...Mouse Origin Bacteria.

Experiment VIII. Intranasal infection with bacteria alone

As control to Experiments VI and VII, 0.5 cc of two percent suspension of various bacteria in sterile physiologic sodium chloride solution was instilled into nostrils of mice under ether anaesthesia. Some of them died within forty-eight hours and the others were killed with ether on the fourth to sixth day after infection. Three mice were infected with pneumococcus type I. No remarkable change was found. Six mice were infected with staphylococcus albus. In these mice lungs, inflammatory changes of interstitium were particularly marked. Seven mice were infected with streptococcus hemolyticus. It caused some kind of interalveolitis, alveolar epithelium increased in number but remained in the usual size. Ten mice were infected with Mouse...
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Origin Bacteria. More conspicuous changes were found in their lungs, leucocytar intraalveolitis was frequently very marked and sometimes peripheral part of it revealed marked polymorphonuclear leucocytar infiltration in interalveolar strands, which, I think, may be call "additional interalveolitis." Bronchitis and inflammatory changes of interstitium were also frequently very marked. But no typical interalveolitis described above was observed in all these control cases.

Experiment IX. Filtration test

Gram-negative coccobacilli were isolated on plain agar from mouse lungs showing catarrhal pneumonia after intranasal inoculation with influenza virus alone (Experiment III). These involved lungs were ground to form suspension in sterile physiologic sodium chloride solution and the suspension was filtered through Berkefeld V. The filtrate was administered to six mice intranasally under ether anaesthesia. They were killed with ether on the fourth or fifth day after infection. No remarkable change, except for the interalveolitis described above was found in their lungs. On the other hand, the suspension was administered to another six mice without filtration. Four mice died within seventy-two hours and others were killed with ether on the fifth day after infection. In addition to the interalveolitis described above, marked catarrhal pneumonia and suppurative changes were frequently found in the lungs of these mice. The results may correspond to those of double infection with virus and bacteria.

DISCUSSION

It has been shown by some previous investigators, Smorodintseff and Ostrovskaya (1937) (11), and Rickard and Francis (1938) (12), that influenza virus administered intravenously or intraperitoneally to mice arrives in their lungs and induces there pulmonary lesions, and the absence of visible alteration in their lungs does not exclude the presence of the virus. But, at that time, they have not examined these lungs microscopically. The suggestion of these investigators that influenza virus may be present, without visible lesions, in the lungs of the mice inoculated with it intravenously or intraperitoneally is supported by the observation made in this work. In my cases of intravenous or intraperitoneal inoculation no visible lesion is observed in the lungs of infected mice but conspicuous changes of alveolar walls, interalveolitis described above, are always found microscopically.

Contribution of Straub (1940)-13 to histopathology of experimental influenza pneumonia is more substantial. According to his report influenza virus administered intranasally to mice affects specifically the epithelium of the respiratory tract and it causes catarrhal bronchitis. But this change is not always found in my study, namely, it is found in the bases of intranasal inoculation but not found in the cases of intravenous and intraperitoneal inoculation. Therefore, it may be concerned with the
route of inoculation. Some other workers, Shope (1931, 1934) (14, 15), and Francis (1935) (16), observed conspicuous changes of alveolar walls in experimental influenza pneumonia using human or swine influenza virus intranasally but they paid no special attention to these changes, for they observed many other changes, bronchitis, inflammatory changes of interstitium, intraalveolitis etc., in the same lungs. It seems probable that in some instances of intranasal inoculation man can not neglect a mechanical influence of fluid instillated into nostril of the mouse and its additional and successional influence, particularly interference of microorganisms living in the respiratory passage of the infected mouse customarily (Olitsky and Gates 1921 (17), Hoyle (1935)). I think, a complicated pulmonary lesion produced by accidental concurrent infection of virus and ordinary bacteria may be found in some previous investigators’ experiments using influenza virus alone intranasally to mice.

The interalveolitis described above is also found in all my cases of intranasal inoculation even when visible lesion is absent. It is never found in any control experiments. Other changes, bronchitis, intraalveolitis (catarrhal pneumonia) and others, are demonstrable only in my cases of intranasal inoculation, but, even in these cases they are not found constantly. Therefore, one may be allowed to say that the interalveolitis described above is the most characteristic change in the lungs of mice inoculated with influenza virus. It is found diffusely and independently, so I suppose, it may belong to the category of “interalveolar pneumonia” proposed by Tanabe (1938) (18). Tanabe explained that the interalveolar pneumonia is not visible in nature. Accordingly, these observations make it clear how the virus can be transferred from mice in absence of visible lesion.

Differentiation between an immediate sequence of infection with influenza virus alone and an effect of a secondary inflammatory process occurring in the diseased parts of the lungs has been not wholly brought to light. A few previous reports concerning this problem are as follows: Numerous polymorphonuclear leucocytes infiltrate in section from lungs in which a bacterial invader has been present (Shope 1934, Straub 1937). Catarrhal pneumonia accompanied by hemorrhage is observed in the lungs of mice inoculated with influenza virus and streptococcus hemolyticus or Bacillus Pfeifferi (Tsurumi and his collaborators 1943 (19)).

In my study, gram-negative coccobacilli are frequently isolated from lungs of mice showing catarrhal pneumonia after intranasal inoculation with influenza virus alone. When these lungs are ground to form suspension and administered intranasally to mice marked catarrhal pneumonia and suppurative changes are often demonstrated in their lungs. But these changes are not observed when the material is given intranasally after filtration through Berkefeld V. In addition to the interalveolitis described above a catarrhal pneumonia accompanied frequently by marked hemorrhage is always found in the lungs of mice infected doubly with influenza virus and some bacteria and sometimes these lungs reveal suppurative changes and marked edema. I suppose that these changes may not be regarded as effects induced by influenza virus alone but are
related to concurrent infection of influenza virus and bacteria. Hemorrhage is generally more marked in the cases of double infection with virus and bacteria than in the cases of inoculation with virus alone. Edema is most conspicuous in the cases of simultaneous double infection with virus and bacteria. It is interesting that the histopathological changes of the lungs of mice infected doubly with human influenza virus and some bacteria is closely resembling those of influenza pneumonia in man.

SUMMARY

1) Interalveolitis characterized by marked reaction of alveolar epithelium is found in the lungs of mice inoculated intravenously or intraperitoneally with human influenza virus (type A).

2) In addition to the interalveolitis described above, bronchitis, inflammatory changes of interstitium and catarrhal pneumonia are observed in some cases of intranasal inoculation with human influenza virus (type A). Gram-negative coccobacilli are frequently isolated from mouse lungs showing catarrhal pneumonia.

3) The interalveolitis is transferred from mice to mice constantly in serial nasal passages.

4) The interalveolitis is found most conspicuously on the fourth day after intranasal inoculation.

5) Together with the interalveolitis catarrhal pneumonia is found in the lungs of mice infected doubly with human influenza virus (type A) primarily and two or three days after with some bacteria secondarily. There are observed frequently marked hemorrhage and sometimes suppurative changes and edema.

6) Approximately identical changes are found in the lungs of mice infected doubly with human influenza virus (type A) and some bacteria simultaneously. But the interalveolitis is less striking and edema is more marked in these instances.

7) A marked catarrhal pneumonia and suppurative changes are frequently found in the lungs of mice inoculated with unfiltered material from which gram-negative coccobacilli are isolated on plain agar culture, while these changes are not found in the lungs of mice inoculated with the material after filtration through Berkefeld V.

CONCLUSIONS

1) Interalveolitis characterized by marked reaction of alveolar epithelium is the most striking feature in the lungs of mice inoculated with human influenza virus (type A). It may belong to the category of interalveolar pneumonia (Tanabe).

2) A mixed type of pneumonia consisting of the interalveolitis described above and a catarrhal pneumonia is found in the lungs of mice infected doubly with human influenza virus (type A) and some bacteria. It is accompanied frequently by marked hemorrhage and sometimes by suppurative changes and edema.

I wish here to express my deep gratitude to Prof. Hiroshi Tanabe for his cordial
REFERENCES

Fig. 1. Mouse lung showing interalveolitis characterized by marked reaction of alveolar epithelium, fifth day after infection with human influenza virus (P.R.8) intravenously.

Fig. 2. Mouse lung showing the interalveolitis described above, fifth day after infection with influenza virus (W.S.) intraperitoneally.

Fig. 3. A mixed type of pneumonia consisting of the interalveolitis and hemorrhagic catarrhal pneumonia. The mouse was inoculated with human influenza virus (P.R.8) intravenously and two days after with Mouse Origin Bacteria intranasally and killed after two more days.

Fig. 4. A mixed type of pneumonia consisting of the interalveolitis and a catarrhal pneumonia (leucocytar intraalveolitis). The mouse was inoculated with human influenza virus (W.S.) intraperitoneally and two days after with Mouse Origin Bacteria and killed after two more days.

Fig. 5. Mouse lung showing a catarrhal pneumonia (leucocytar intraalveolitis) and intense infiltration with polymorphonuclear leucocytes in interalveolar strands, third day after infection with Mouse Origin Bacteria.