INFECTIONOUS CATARRH OF MICE

I. A NATURAL OUTBREAK OF THE DISEASE

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In an earlier report the etiology of a fowl coryza or catarrh of slow onset and long duration was ascribed to certain minute Gram-negative cells descriptively referred to as coccobacilliform bodies. It was of interest to determine whether these bodies, which are unlike any of the known infective agents, were associated with catarrhal states in other hosts. In looking about for suitable material for study an infectious catarrh which met the essential requirement of being readily transmissible was unexpectedly encountered in mice. The nature and etiology of this disease, which it appears has not been previously described or at least not recognized as a distinct entity, are discussed in this and the succeeding papers.

In May, 1935, a group of Swiss mice was brought to The Rockefeller Institute in Princeton, N. J., to replace a breeding colony which had been found to harbor the virus of acute lymphocytic choriomeningitis. The Swiss breeders together with the accumulated young were held under strict quarantine. Aside from periodic inspections, no one but the attendant came in contact with the colony.

The breeders were divided into groups of 5 females and 1 male. The young were born in the breeding cages and kept there until weaned during the 3rd or 4th week of life. The weaned mice were segregated as to sex in groups of 20–25 individuals. They proved to be particularly poor experimental subjects, being jumpy and irritable. The total population fluctuated somewhat but generally numbered at least 400 breeders and an equal number of young.

In the fall of 1935 we had occasion to examine the nasal passages of several young Swiss mice that had been used experimentally and found a pronounced

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in each animal. Other mice taken directly from the colony likewise showed a nasal inflammation and in addition were observed to make a peculiar chattering noise. An inspection was made of the colony, particular attention being paid to the breeders. At this time there were 75 cages of adults comprising a total of 450 mice. 88 of these mice were chattering when examined. A considerable number of chatterers were also noted among the young mice. During the succeeding month 30 infected mice, 14 of which were breeders, were autopsied. All but one of these mice were chatterers and all but one also showed a rhinitis. A pneumonia was found in 5 animals.

The death rate was low at this time. A considerable number of the older animals, however, had a ragged appearance with ruffed coats. As indicated by an increase in the number of chattering mice the disease continued to spread through the colony. Entering the room where the mice were isolated one was immediately impressed by the simultaneous chattering of many animals. During the latter part of February, 1936, an inspection was made of the young mice. At this time there were 27 cages of mice that had been weaned from 1-7 weeks. In each of the cages, which averaged 20 mice to the cage, there was at least one chatterer, the number varying from 1 to 6. The spread of the disease was so great that it seemed advisable to dispose of the colony and early in March this was done, all of the animals being killed with the exception of a group of 75 that was withheld for observation.

**Symptoms of the Disease**

Chattering was generally the first apparent symptom of the disease and, while usually coincident with a rhinitis, was sometimes noted in its absence. The nasal inflammation was never accompanied by a discharge either post mortem or during life. Early in the disease, as indicated by observations on recently weaned mice, the chattering was commonly low and intermittent, requiring close inspection for its detection. Snuffling, a distinctly different sound, was also characteristic of the disease. The act of rubbing the front paws over the nose was somewhat more frequent with infected mice than with normal individuals. As the disease progressed the chattering generally became more distinct and regular. The sound of chattering is difficult to describe but somewhat resembles that made by gently clicking the teeth. The sound apparently arises from the lower part of the respiratory tract.

Other symptoms varied considerably with different individuals. A few infected mice showed a loss of weight almost from the onset. Their coats were ruffed, their respiration rapid and shallow, and they
died 3–5 weeks after the appearance of chattering. Many infected mice, however, appeared normal, aside from chattering, for weeks. Their coats were sleek, they gained weight normally, were active, and the females reared their young successfully. Eventually these animals developed the same symptoms and died. Mice in which the disease had progressed slowly over a period of months showed considerable loss of hair, together with a scabby skin and not infrequently marginal necrosis of the ear. Whether these latter symptoms are part of the disease or incidental to it is uncertain.

The Mortality of Naturally Infected Mice

Early in March, 1936, shortly before the colony of Swiss mice was disposed of, a group of 75 animals was removed to a quarantine unit and held under observation. This group included 53 infected breeders of both sexes, all of them chatterers, and 22 young mice approximately 6 weeks old. The young mice, which had been kept together since they were weaned, were removed at random from the stock; 3 of them were chatterers, the others symptomless. The breeders were divided into 3 groups which were held in the same cages during the period of observation.

The deaths which occurred among these mice are recorded by months in Table I. The breeders began to die during the 1st month after isolation and by the end of the 4th month 60 per cent had succumbed. How long the breeders had been infected when the period of observation was begun is not known. At the end of the 11th month, when the experiment was discontinued, there was only one survivor in this group.

<table>
<thead>
<tr>
<th>Class</th>
<th>No. of mice</th>
<th>No. of deaths by months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breeders</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Young</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>9</td>
</tr>
</tbody>
</table>

The Monthly Incidence of Mortality in Naturally Infected Mice

TABLE I
No deaths were recorded among the young mice until the 2nd month of isolation. The lag here may be accounted for by the fact that only 3 of these animals showed obvious symptoms of the disease when first isolated. At the end of the period 2 of the young mice were still alive.

Because of the condition of the mice when found comparatively few autopsies were made on either the breeders or the young mice. Animals which were examined showed typical manifestations of the disease and invariably a pneumonia. Late symptoms of the disease were obvious in many of the animals prior to death. The mortality incidence which may be regarded as essentially specific was 96 per cent for the entire series of 75 mice during the isolation period of 11 months.

Experimental Transmission of the Disease

Observations on the experimental transmission of the catarrh were delayed by the lack of disease-free animals. Mice of known history were not regularly available until January, 1936. The mice that were finally used came from the same stock as the original colony, in which meningitis had been detected. When this colony was discontinued a small group of pregnant females was withheld. From these a nucleus of meningitis-free mice was obtained by selective breeding. Symptoms indicative of the catarrhal disease had never been observed in the parent colony, and young mice from the selected group likewise appeared to be uninfected. Between January, 1936, when transmission experiments were begun and January, 1937, 101 young mice which showed no symptoms of the disease were autopsied. In all animals the middle ears, nasal passages, and lungs were normal. All but 10 of these mice had received a nasal instillation under ether of some material of suspected pathogenicity. The series constitutes an excellent check on the freedom of the mice from the specific disease and on the innocuousness of the instillation procedure when uninjective material was employed.

Mice from the selected colony proved to be highly susceptible to the disease. It was readily and invariably transmitted by the nasal instillation of exudate removed from the upper air passages of naturally infected animals. Maintenance of the disease by the serial passage of exudate from affected to susceptible mice was also accomplished. 6 successive passages were carried out between Oct. 16, 1935, and May 5, 1936, employing a total of 32 mice. The incidence

Under the direction of Dr. Traub.

A few mice from the selected colony were available in October, 1935.
of disease in this series was 100 per cent. All of the injected mice showed a rhinitis which was accompanied by chattering in 31. 25 of the animals also showed a pneumonia. The middle ears of only 15 of the mice were examined at autopsy; of these, 14 showed an otitis media which was generally bilateral.

In making the nasal instillations pooled exudate, removed at autopsy from the upper air passages of several infected mice, was generally used. The exudate was well mixed with 0.5 cc. of sterile saline. Young mice, 16-20 gm. in weight, were employed. After being deeply etherized, the exudate suspension was administered to them with a capillary pipette, 6-10 drops being placed on the nares. If the animal is well anesthetized the fluid is promptly drawn into the nasal passages without bubbling or sneezing. Usually 4 mice were injected at a time and kept together in the same cage for the duration of the experiment. They were examined regularly after the 1st week, during which time they are commonly symptomless, and were usually brought to autopsy in the 3rd or 4th week after injection.

The symptoms of the disease in experimentally infected mice were identical with those in naturally infected animals. Since most of these mice were killed 3-4 weeks after injection the disease was generally manifested only by chattering. The few mice which did succumb during the period of observation showed the usual loss of weight and ruffing of the hair. Chattering was usually apparent by the 10th to the 14th day after injection. At this time, however, it was commonly light and intermittent, requiring close observation for detection. Later the chattering became louder and more regular.

For some time it was thought that a conjunctivitis was a frequent sign of the disease in injected mice. It was shortly found, however, that uninjected mice removed directly from the stock colony showed symptoms which simulated a conjunctivitis. There was a copious lacrimation with wetting and matting of the hair adjacent to the eye; in some mice there was a distinct ring around the eye. At times the eyelids were swollen and flecked with a white deposit. With a capillary pipette a small amount of chalky fluid could be aspirated. No periorbital swelling was noted. Stained films of the fluid showed numerous epithelial cells but no leucocytes. This condition, the precise nature of which is unknown, may persist for weeks. An occasional injected mouse may, however, show a true conjunctivitis, in
which case the symptoms are identical but films show leucocytes and in addition certain minute Gram-negative coccoid bodies which will be discussed later.

Exudate from the middle ears of mice with an otitis media and suspensions of ground lung from mice with a pneumonia were also infective when administered intranasally. Mice injected in this way showed typical symptoms and postmortem manifestations of the disease.

**Postmortem Manifestations of the Disease**

The most significant manifestations of the disease were observed only at autopsy. The following summary of the postmortem findings is based on 45 complete autopsies. This group comprises both naturally and experimentally infected animals, the disease being induced in the latter either by the nasal instillation of exudate or by contact.

Forty-three of the infected mice (95 per cent) showed a rhinitis. This condition was never accompanied by a nasal discharge during life. Generally a diagnosis could not be made by macroscopic inspection of the exposed nasal passages but was readily made by aspiration with a capillary pipette. Usually only a small amount of thick mucus which was commonly mixed with blood, as the procedure causes some bleeding, could be removed from the nasal passages of normal mice. From infected animals a copious, semifluid, white exudate of a mucopurulent nature was generally withdrawn. Since only a light suction is necessary for its removal the exudate was rarely mixed with blood. Stained films of the material from normal mice showed scattered epithelial cells and few or no leucocytes, depending on how much blood was present. Films of exudate showed numerous leucocytes together with varying numbers of epithelial cells and strands of mucus. In a few mice the exudate was scanty and contained blood, requiring a microscopic examination for diagnosis. If the material was inflammatory in origin it invariably contained large numbers of leucocytes in nearly every microscopic field. 2 of the mice in this group showed no macroscopic or microscopic indication of a nasal inflammation.

Forty-three of the mice also showed an otitis media, which was bilateral in all but 3 animals. The only outward indication of a middle ear involvement was a bulging of the tympanic membrane. This state, however, was rarely observed. Twisting or rotating has never been noted in affected mice from either the selected or the original Swiss colony. The presence of exudate in the middle ear cavity, which was exposed by cutting through the tympanic bone after removal of the lower jaw, could generally be determined by inspection. The exudate was often copious and typically purulent showing numerous leucocytes microscopically.
A pneumonia was encountered in 35 (77 per cent) of the 45 infected mice. It was usually lobar in distribution; the affected lobe was consolidated, somewhat contracted, and red, gray or mottled in color. Less commonly the pneumonia was patchy, in which case marginal areas of involvement were most often observed. Such areas were sharply demarcated from the normal lung tissue. Abscess formation has never been observed even in advanced cases. Many of the mice in this group were killed 3-4 weeks after injection. In these animals the pneumonia was generally limited to one or two lobes, commonly one of the three right lobes or the small azygous lobe. Adjacent unconsolidated lobes were sometimes definitely emphysematous. From observations on naturally infected mice which were held for a much longer period, it was apparent that the pneumonia was progressive, affecting more and more lung tissue and finally resulting in death of the animal. In mice which had succumbed it was not unusual to find all three right lobes, the median, and part of the large left lobe pneumatic.

Histologically the pneumonia appears to be initially a bronchial involvement with a secondary alveolar extension. Sections show a partial plugging of the bronchi with an exudate composed chiefly of polynuclear leucocytes. There is usually a hyperplasia of the peribronchial lymphoid tissue. The appearance of the parenchyma varies from case to case. The alveoli often contain leucocytes together with red blood cells and large mononuclear cells. In some cases the alveolar walls are distended and there is evidence of fluid in the alveolar spaces.

Communicability of the Disease

The rapid spread of the disease in the original mouse colony indicated that it was readily communicable. It appears probable that direct contact is the significant means of transmission and that indirect contact is relatively unimportant. Cages of normal mice have been kept repeatedly and for considerable periods of time in the same room with many cages of diseased animals without cross infection. No particular precautions were observed in handling the cages. None of the normal mice that were so exposed showed either symptoms or postmortem manifestations of the disease.

That the catarrh was experimentally transmissible by direct contact was shown by 5 experiments in which normal mice were directly exposed to either naturally or artificially infected animals. 27 mice were employed in the 5 experiments. The incidence of infection in these animals was 100 per cent. The onset of the disease was somewhat more gradual than that of mice infected by nasal instillation and its progress was slower. The result, however, was the same; if the experiment was maintained long enough the disease terminated fatally.
In one experiment 6 normal mice were placed in the same cage with 4 naturally infected animals. Chattering was first observed on the 25th day of exposure. 4 of the mice which had shown the usual late symptoms of the disease died during the 18th, 19th, 22nd, and 23rd week, respectively. The only one of these mice which was autopsied showed an extensive pneumonia, a bilateral otitis media, and a rhinitis. The 2 survivors were killed during the 24th week with similar postmortem findings.

In a second experiment 6 normal mice were placed in direct contact with one infected mouse from the preceding group. The exposed mice began to chatter on the 29th day. 5 of these mice which were chattering but otherwise symptomless were killed during the 15th to 19th weeks. All of them showed a rhinitis and an otitis at autopsy. There was no evidence of pneumonia. The 6th mouse was held for further observation. It soon began to lose weight and died during the 26th week. At autopsy there was an advanced pneumonia in addition to a rhinitis and an otitis.

DISCUSSION

The disease of mice described herewith resembles the infectious coryzas of chickens in being essentially an inflammatory response to a specific irritant of surface epithelium. In its slow onset it also resembles the type of fowl coryza which is caused by the minute cells referred to as coccobacilliform bodies. In chickens affected with this type of coryza, however, the inflammatory reaction is generally limited to the nasal passages; the trachea is occasionally involved but the lung is invariably unaffected. In mice the inflammatory reaction is rarely so localized. There is generally an extension of the reaction from its initial locus in the nasal passages to the middle ears and to the lung. In chickens the coryza of slow onset is persistent and a nasal discharge may continue for weeks. It is not fatal, unless complicated by other factors, and if infected birds are held long enough they recover. It appears probable that establishment of the infective agent in mice is always followed by a pneumonia of slow progression which is ultimately fatal.

The mouse disease is attended by relatively few symptoms. Chattering may be the only early means of recognition, but even it is occasionally lacking. Later in the disease constitutional disorder is manifested by loss of weight, inactivity, ruffling of the hair, and altered respiration.

The disease is experimentally transmissible by nasal instillation and
is communicable by direct contact. Under natural conditions it may be epidemic, as was the case in the mouse colony here reported. Experience with another stock of mice, formerly maintained at The Rockefeller Institute in Princeton, indicates that the disease may also be endemic. Chattering mice were observed from time to time in this colony but were never numerous. At autopsy these mice also showed a pneumonia and an otitis media but their nasal passages were normal. The absence of a rhinitis may have been a factor in limiting the spread of the disease.

Whether this disease is in any way related to the so called mouse influenza recently reported in Germany by Kairies and Schwartzè cannot be stated at this time. Recognition of these native murine infections is of no little importance in view of the emphasis placed on mice in the study of certain virus diseases of man.

SUMMARY

A natural outbreak of an infectious catarrh in a colony of Swiss mice is reported. The disease was generally characterized by a peculiar chattering sound during life and by a rhinitis, an otitis media, and a pneumonia at autopsy. The pneumonia was slowly progressive and terminated fatally in a high percentage of cases. The mortality in a group of 75 naturally infected mice was 95 per cent over a period of 11 months.

The disease was readily reproducible in susceptible mice by the nasal instillation of exudate from any locus of infection. It was also transmissible by direct contact. In both naturally and experimentally infected animals there was an incubation period of 10 days or more before symptoms were apparent. Recovery from the disease was not observed.

EXPLANATION OF PLATE 27

Fig. 1. A mouse infected with catarrh; showing characteristic posture, ruffling of the hair, and abrasions about the ear.

Fig. 2. A section through the bronchus in a consolidated lobe of the lung of an infected mouse. Stained with phloxin-methylene blue. $\times$ 105.

Fig. 3. Distribution of polynuclear leucocytes in exudate from the nasal passages of an infected mouse. Gram stain. $\times$ 370.

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