STUDIES ON THE ETIOLOGY OF SNUFFLES IN STOCK RABBITS.

PARANASAL SINUSITIS A FACTOR IN THE INTERPRETATION OF EXPERIMENTAL RESULTS.

BY JAMES E. McCARTNEY, M.D., AND PETER K. OLITSKY, M.D.

(From the Laboratories of The Rockefeller Institute for Medical Research.)

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INTRODUCTION.

With the hope of throwing more light on the group of upper respiratory diseases in man, we have sought to study a similar affection in laboratory animals,—rabbit snuffles. In choosing this subject, it was apparent that there would be no lack of material because snuffles is almost ubiquitous among stock rabbits, occurring in endemic form practically all the time, and in epidemic form at periodic intervals. Furthermore, the study concerned an ailment, the incitant of which is still in doubt, although some affirm Bacillus bronchisepticus, and others Bacillus lepisepticus, as the etiological agent. In view of the prevalence of the disease and the frequency with which the rabbit is employed in experimental work, additional findings in this field should prove of importance to the laboratory worker.

Literature Regarding Etiological Agents.—Bacillus lepisepticus is regarded as the incitant of rabbit snuffles by Beck, Kraus, Roger and Weil, Volk, and others. Bacillus lepisepticus, first accurately described in 1887 by Theobald Smith, is now classed with the Pasteurella or hemorrhagic septicemia group of microorganisms. An examination of the articles quoted shows that in no instance has uncomplicated rabbit snuffles, free from septicemia, been induced with this bacillus. Indeed, in the hands of some investigators, as, for example, Volk, this

1 Beck, M., Z. Hyg., 1893, xv, 363.
2 Kraus, R., Z. Hyg., 1897, xxiv, 396.
organism, when applied to the uninjured nasal mucous membranes of rabbits, fails to cause snuffles; applied, however, to the scarified mucosa, it induces death, apparently from septicemia, but without clinical signs of snuffles. Similarly, Roger and Weil's experiments demonstrate that this bacillus causes experimental rabbit septicemia which, only at times, is associated with what appears to be a symptomatic rhinitis.

On the other hand, an organism first described by Tartakowsky, and rediscovered by Ferry in 1910 as the supposed cause of canine distemper, called by the latter Bacillus bronchisepticus, was considered later (1912) by Ferry and by M'Gowan and by Ferry and Hoskins as the incitant of snuffles. In the words of Ferry and Hoskins: “It seems to be evident that the ordinary form of snuffles as encountered in the various rabbitries in this country, characterized by a variable nasal discharge accompanied by sneezing and rubbing the nose, with more or less loss of appetite and weight and a rather subacute or chronic course (which constitutes the large majority of cases), is caused by *B. bronchisepticus*; while the more acute form and the most fatal, in the majority of instances is due to *Bact. lepisepicu*m.” These writers do not believe that snuffles is a single entity, and quote Ward who could produce snuffles by injecting rabbits intravenously with either *Bacillus ozaena, Bacillus proteus*, or *Bacillus bronchisepticus*.

A number of other microorganisms has been described by different investigators as causing rabbit snuffles, but the literature fails to confirm their specific relationship.

It appears then from the work of previous writers that the question as to the actual causation of rabbit snuffles is still unanswered. Furthermore, there is no clear conception of the definition of the uncomplicated disease. One group of investigators who maintain that *Bacillus lepisepicu*m is the etiological agent regards snuffles as a stage or symptom of septicemia.

The investigations reported in this paper have to do with snuffles as it occurs among laboratory stock rabbits. We shall first describe the disease encountered in such animals so as to present the basis on which our experiments were made.

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Description of the Disease.

Snuffles as it occurs spontaneously in rabbits kept under laboratory conditions may be divided clinically into different groups: the intermittent and the chronic, which are the commonest types, and the acute, which is infrequent.

Intermittent snuffles is to be noted especially in rabbits which are observed over long periods—many months or even years. A typical attack begins with an acute nasal discharge of a slight amount of thin mucus, which may be transitory and can scarcely be called snuffles. In some cases, the process may go on to a mucopurulent or purulent stage with sneezing, rubbing the nose, soiling and consequent matting of the hair of the paws, loss of appetite and of weight. After a number of days, these symptoms subside and the animal returns to normal apparently. Under conditions which reduce the resistance, to be described later, as also spontaneously, several attacks may occur in the course of a year.

In the chronic form of snuffles, the rabbit has a persistent, white, tenacious, nasal discharge accompanied frequently with crust formation on the nostrils. There is to be noted sneezing when nasal obstruction is present, along with rubbing of the nose and soiling and matting of the hair of the paws which are frequently depilated in small areas. The disease may progress to a destruction of the nasal bones with a deformity simulating in outward appearance luetic destruction of the nose in man. Infrequently there forms a localized abscess about the nasal fossae. The animal may become adapted to this chronic condition so that there is little, if any, loss of weight, or emaciation.

The acute variety is not common, to judge from our experience with stock rabbits of 800 to 3,000 gm. or more in weight, and a few months to several years of age. Indeed, we believe that this condition can best be seen in breeding establishments where animals are observed from the first weeks of life. When it does occur among laboratory stock it is a manifestation of some underlying disease, such as septicemia. In these cases there is a thin, glairy discharge from the nose, and a rapid weakening of the animal leading to death. From the nasal discharge, blood, and organs, especially the lungs, *Bacillus lepisepticus* can be isolated. Or the acute attack may accompany...
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pneumonia or other infections and resemble the nasal disorder occurring in a variety of primary conditions such as hay-fever, common colds, influenza, the exanthemata, and seen after exposure to irritants or cold, in man. The failure to distinguish acute, uncomplicated snuffles from the nasal disorder secondary to some underlying disease has led some previous investigators into error when they ascribed to the incitant of snuffles, the etiological agent of the disease responsible for the false "snuffles" they observed.

Sinusitis in Snuffles.

In early experiments we noted the frequency of paranasal sinusitis in apparently normal animals and in those suffering from snuffles. This condition interfered with our procedures to such an extent that an extensive study was begun to determine its nature.

Anatomy of the Rabbit's Nose.—The frequency with which the rabbit suffers from nasal affections is probably due to the complexity of the nasal passages.

The turbinate bones which contain numerous folds are situated on the posterior and lateral walls. The maxilloturbinate, a finely ridged mass of bone, occupies the anterior portion of the lateral wall, while the ethmoturbinate, which consists of much broader folds, is placed posteriorly. Each of these folds or serrations is covered with nasal epithelium so that numerous pockets are present. Moreover, the nasolachrimal ducts discharge into the nasal passages. Besides these structures there are various paranasal sinuses. Congestion of the mucous membrane with resultant swelling may convert the folds or sinuses into closed cavities, thus permitting infectious processes or purulent material to remain localized. The tendency for closed pockets of infection to develop has, we believe, a considerable bearing on the production of the clinical condition known as snuffles and on the interpretation of the results of experimental inoculation.

Occurrence of Sinusitis.—A systematic examination was made of the upper air passages of thirty-four rabbits, among which were animals with snuffles. Included in this number were carefully selected normal rabbits which had been under observation for several months.

The examination included a thorough investigation of all the organs including the brain. The nasal passages were exposed by cutting away the bones of the nose and frontal region of the skull. In order to avoid irritation of the mucous membrane by general anesthetics, such as chloroform or ether, the rabbits were killed by quickly severing the upper cervical spinal cord.
Of the thirty-four rabbits, twenty-three were found to be suffering from intermittent or chronic snuffles. Of these latter, twenty-two had a chronic inflammation of the mucous membrane of the upper nasal passages associated with a purulent paranasal sinusitis.

In the cases of long duration, all the sinuses were filled with thick, white, tenacious, inspissated, odorless pus; while in those of shorter duration only one or two sinuses were so affected. The mucous membrane lining the turbinates and the sinuses was thickened but showed no signs of congestion or acute catarrhal inflammation. In some instances, the thickening of the mucosa resulted in a pocket, the opening of which revealed the firm pus already described. On microscopic examination, the epithelial cells were seen to be necrotic and exfoliated in areas. The subepithelial zone was thickened by an extensive exudation of polymorphonuclear and endothelial leucocytes, or monocytes, but without congestion. Some edema was also present, and in Giemsa-stained preparations, bacteria were noted in the ciliary layer and in the subepithelial zone, mainly phagocytosed. Giemsa's, Gram's, and methylene blue stains of the pus showed numbers of mononuclear cells and somewhat less abundant, polymorphonuclear elements. Many of these cells were disintegrated like those in the pus found, as a rule, in chronic infectious processes. That is, the cell outlines were blurred, the nuclei indistinct, and the cell granules few in number. Numerous broken down cells with granules liberated and scattered were seen. Few bacteria, but these often of different species, were found in phagocytosis as well as outside the cells. The culture findings will be described further on.

Of the thirty-four rabbits, two showed signs of slight snuffles, that is, there was no actual nasal discharge, but merely a dampness about the nostrils, and some sneezing, but none of the other signs of a typical attack, as, for example, soiling or matting of the hair of the paws. Such cases are usually designated in the literature as "beginning snuffles." In both instances was found a chronic inflammatory process of the mucosa and sinuses similar to that met with in chronic snuffles.

Of the original series, nine rabbits were carefully selected as having no ailment whatever, and certainly no obvious signs of nasal affection. These animals were under observation for several months, and were regarded as normal stock. Two of the nine showed the chronic inflammatory process of the mucosa of the nasal passages associated with the purulent sinusitis above described, which is similar in its pathological picture to that exhibited by the animals with typical chronic snuffles.
In another series of 121 rabbits which were carefully selected, individually caged, and kept under a rigid quarantine, five showed moist noses, or what might be considered as slight snuffles. In these five, chronic sinusitis was found. Among the remainder, carefully examined for any possible indication of past or present disease, and determined by this rigid test to be outwardly normal, nine revealed a chronic inflammatory condition of one or more of the nasal sinuses.

Bacteriological Examination.—As Ferry and Hoskins pointed out there is no one organism constantly associated with the condition known as snuffles, although they believe *Bacillus bronchisepticus* causes the chronic, and *Bacillus lepisepticus* the acute disease.

In the present study, the material constituting the nasal discharge was obtained during life by means of a swab, and at autopsy the pus from the sinuses and nasal passages was secured. The nasal discharge and pus were stained and examined microscopically for bacteria and cellular elements. Cultures were made by streaking the pus on rabbit blood agar plates which were incubated for 24 to 48, or more hours, at 37°C.

It may be stated that no one organism was found constantly associated with the condition. The commonest microorganisms isolated were, in the order of their frequency, *Staphylococcus albus, Bacillus bronchisepticus, Bacillus lepisepticus, Micrococcus catarrhalis, a hemolytic mucoid, Gram-negative bacillus, a diphtheroid, and other unidentified bacteria occasionally*. Stained film preparations of the nasal discharge and pus from the upper passages showed, as a rule, an extensive degeneration of cells and a limited phagocytosis of microorganisms, features indicating, as already described, that the exudates were chronic in nature.

When more than one sinus is involved, different bacteria may be present in the various sinuses, as the following protocol illustrates.

*Rabbit SA*, a stock animal, suffering from snuffles of unknown origin and duration, was killed by pithing. The orbital sinus contained thin, glairy pus which yielded a pure culture of a hemolytic mucoid organism resembling those of the Friedländer group of bacilli. The paranasal sinus was filled with thick,
white, tenacious, inspissated pus from which a pure culture of *Bacillus bronchisepticus* was obtained. The anterior nares, on the other hand, contained thick, white pus which on culture showed a mixture of both of the microorganisms mentioned.

In this instance, illustrative of other findings, the chronic sinusitis in different regions was associated with two distinct bacteria.

In later observations on more than 50 rabbits the incidence of chronic sinusitis was found to be still greater than in those first studied, both as concerns apparently normal animals and those showing chronic, intermittent, or beginning snuffles.

To summarize, it appears that practically 100 per cent of stock rabbits suffering from chronic, intermittent, or beginning snuffles reveal old, chronic, inflammatory processes of the upper nasal passages, while 9 per cent of apparently normal stock animals, free from any symptoms whatever, exhibit similar chronic purulent conditions of the upper nasal passages. Ordinarily, on casual selection of supposedly normal rabbits, this proportion is still higher and may reach 25 per cent of the total. The bacteria most commonly met with are *Staphylococcus albus*, *Bacillus bronchisepticus*, and *Bacillus lepisepticus*. In other words, in about one-tenth of a carefully selected group of normal stock rabbits and in as many as one-fourth of a casually selected group, chronic infectious processes involving one or more of these microorganisms can be found in the nasal passages, *before any experimental procedure is begun*.

*Transmission Experiments.*

The facts already presented show the difficulties of interpretation of experimental procedures to induce snuffles. It is desirable, before stating our attempts at transmission, to direct attention to certain other factors which may favor the spontaneous onset of the disease, or symptoms simulating the affection. Dust or mould in samples of defective hay, employed for feeding purposes, may give rise to acute irritation of the nasal passages associated with a certain amount of mucoid discharge and also with conjunctivitis. This condition appears to be due purely to mechanical irritation and not to infection. The disease itself may be induced in apparently normal animals by lowering the resistance, as by subjecting them to low temperatures. An analogy can be found...
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in the experiments of Mudd and his coworkers \(^\text{14}\) in which it is demonstrated that chilling the body surface of man may induce "colds." Another factor in reducing the resistance of rabbits is the injection of killed vaccines.\(^\text{15}\) In view of the presence of chronic disease in the nasal passages of rabbits supposedly normal, it is presumed that lowering the resistance of the animals causes an extension or increase of the previously existing inflammatory process, thus converting what may be termed a potential snuffles into an active and intermittent type of the disease.

The importance ascribed to \textit{Bacillus bronchisepticus} and \textit{Bacillus lepisepticus} as the etiological agents of rabbit snuffles suggested to us an attempt to induce the disease de novo with these cultures, with due regard for the factors which might interfere with the experimental results.

\textit{Experiments with Bacillus lepisepticus Cultures.---}A pure culture of \textit{Bacillus lepisepticus} \(^\text{16}\) was employed in the following experiment. It was originally obtained from snuffles secretion and its virulence had been enhanced by intrapleural passage through twelve consecutive rabbits.

Thirteen young rabbits (about 800 to 1,000 gm. in weight) were used. These were selected because such are said to be especially susceptible to this microorganism\(^\text{17}\) and also to exclude, if possible, previous attacks of snuffles. The material inoculated consisted of a heavy suspension (about 5,000 million per cc.) of an 18 hour growth on blood agar seeded directly from the pleural exudate of the twelfth rabbit. 0.5 cc. of the bacterial suspension was forcibly injected into each nostril by means of a 1 cc. syringe.

Only three of the rabbits showed symptoms of snuffles which appeared on the 6th, 13th, and 13th day, respectively, after inoculation. On these days the rabbits were killed. The autopsy of the first animal revealed thick, white, inspissated pus in the left nasal sinus, and the mucous membrane of the anterior nares


\(^{15}\) For example, of two rabbits injected intravenously with killed cultures of \textit{Bacillus bronchisepticus} and of four injected subcutaneously with vaccines of \textit{Bacillus lepisepticus}, all showed typical snuffles after two to six inoculations at a time when the serum contained agglutinins against these microorganisms in titers of 1:150 to 1:500.

\(^{16}\) This culture was obtained through the kindness of Doctor L. T. Webster.

was slightly injected. In stained film preparations of the pus, mononuclear cells predominated over the polymorphonuclears. Most of the cells were degenerated: they were poorly and irregularly stained, the nuclei were indistinct and the granules few in number. There were a few small bacilli present, mostly in various stages of phagocytosis. Cultures yielded hemolytic, mucoid, Gram-negative bacilli in pure state but no Bacillus lepisepticus. In the second rabbit there was marked coccidiosis of the liver. A small pocket of inspissated pus was noted in the right nasoturbinal region, but no congestion of the mucosa. Cultures of the pus showed Bacillus lepisepticus. The third animal had only a slight mucopurulent discharge from the nose without involvement of the sinuses.

Ten of the animals of this series remained free from snuffles from 8 to 10 days after inoculation. They were all killed at the end of the period of observation to determine the presence of sinusitis. Six were normal, but in the other 4, chronic inflammatory conditions were found in the mucous membranes of the upper nasal passages, together with inspissated pus in the orbital and nasal sinuses of one, and in the nasal sinus alone in the remaining three. From the pus of one of these three, no growth was obtained; from that of the second, both Bacillus bronchisepticus and Staphylococcus albus were isolated, and from that of the third, a hemolytic, mucoid, Gram-negative bacillus was cultured. The rabbit in which both orbital and nasal sinuses were affected showed in the pus of the orbital sinus Bacillus bronchisepticus, and in that of the nasal sinus Bacillus lepisepticus.

From the foregoing experiments, it will be noted that of thirteen animals inoculated intranasally with a heavy dose of a culture of Bacillus lepisepticus, highly pathogenic for rabbits, only three exhibited snuffles. In two of these three a sinusitis was found, the pathological picture of which revealed an inflammatory condition of long standing, probably antedating the inoculations. From the pus of one of the sinuses, Bacillus lepisepticus was recovered, but from that of the other, a different bacillus was isolated. The third rabbit showed no chronic inflammation of the upper nasal passages but a considerable time, 13 days, had elapsed between the injection of Bacillus lepisepticus and the onset of symptoms. Ten rabbits remained free from snuffles, but in four of these chronic sinusitis was found, associated with various bacteria. An animal showing two distinct sinus infections had different organisms in the sinuses.

We conclude therefrom that Bacillus lepisepticus cannot, by itself, be considered as the incitant of snuffles, for, if a group of supposedly normal stock rabbits be observed over the same length of time em-
ployed in our experiments, findings like those in an inoculated group can be obtained even without manipulation, as we have demonstrated.

We now attempted transmission experiments with *Bacillus bronchisepticus*.

**Experiments with Bacillus bronchisepticus Cultures.**—Our experience with this microorganism closely resembled those with *Bacillus lepisepticus*.

Of six young rabbits inoculated intranasally, in the manner already described, with a culture of *Bacillus bronchisepticus* in its second generation or first subplant from the growth obtained from snuffles material, only one animal exhibited the disease. This took the form of a slight mucopurulent discharge from the nose, which appeared 10 days after inoculation and lasted for 1 day, after which the rabbit returned to normal. The animals were observed over a period of 5 weeks.

As with *Bacillus lepisepticus*, these results indicate that *Bacillus bronchisepticus* cannot be considered as having a specific relationship to the initiation of snuffles in supposedly normal stock rabbits. It is possible, in view of the evidence already presented, that the induction of transitory snuffles in one instance is apparently due to an acute exacerbation of a chronic inflammatory process in the nasal passages, present prior to the experimental procedure.

Attempts to induce snuffles by the inoculation of these supposed etiological agents having failed, experiments were now made in which the nasal discharge itself, or suspensions of the nasal mucosa from typical cases of the disease in stock rabbits were employed. It was thought that perhaps some non-cultivable agent in these secretions, or the conjoint action of *Bacillus bronchisepticus*, *Bacillus lepisepticus*, and *Staphylococcus albus* which were present in them, could operate to induce the disease.

**Experiments with Unfiltered Nasal Secretions.**—Two series of experiments were made.

In one series, the nasal secretions from recent and old cases of snuffles were collected by means of a thin cotton nasal swab and then this material was introduced into the nasal cavities of young, supposedly normal stock rabbits.

In another series, the snuffles animal was killed by pithing, or a blow on the head, and the entire length of the nasal mucous membrane was dissected out. This was then ground with sand and 10 cc. of saline solution, and 0.5 cc. of the supernatant fluid injected into each nostril by means of a syringe.
Altogether, material was employed from twelve rabbits with early snuffles; that is, animals killed after the onset of the first definite symptoms of the disease. It was inoculated into twenty-two young rabbits.

Of the twenty-two animals, seven showed clinical snuffles. Of these, six were killed and all showed a marked chronic inflammatory process in the nasal passages with suppuration in one or more sinuses. Table I summarizes the results in the seven positive cases.

In this experiment, as in the preceding ones, no definite evidence of the transmissibility of the disease by means of the nasal secretions from snuffles could be obtained. For in six of the seven positive cases, were found old, chronic affections in the nasal passages. From the pathological findings of thickened mucous membrane and inspissated pus in the sinuses, containing cells in varying stages of degeneration with relatively few bacteria, mostly phagocytosed, we infer that this nasal condition antedated the inoculation. Furthermore, the irregularity in the period of incubation and the inconstant presence of any one or any single group of microorganisms, together with the preexisting chronic disease of the nasal passages in supposedly normal controls, all indicate that the inoculations were not specifically related to the appearance of snuffles. The evidence supports our earlier observations

### Table I

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Time after inoculation snuffles appeared (days)</th>
<th>Sinus infection (Right, Left)</th>
<th>Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>10</td>
<td>0 0</td>
<td>Bacillus bronchisepticus, Bacillus lepisepticus, and Streptococcus viridans.</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>+ 0</td>
<td>Bacillus bronchisepticus.</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>+ +</td>
<td>&quot; leptisepticus and coliform organism.</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0 +</td>
<td>Staphylococcus albus; few Bacillus bronchisepticus.</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>+ +</td>
<td>Bacillus bronchisepticus; few Staphylococcus albus.</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>+ +</td>
<td>&quot; bronchisepticus, Bacillus leptisepticus, and Staphylococcus albus.</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>+ +</td>
<td></td>
</tr>
</tbody>
</table>

* Rabbit 1 showed snuffles 10 days after inoculation. The symptoms consisted of a scanty mucopurulent discharge which disappeared in 3 days. The animal was not killed.
that the inoculations incite a latent condition to become an active
disease.

Although the unfiltered material failed to give conclusive results,
we now used filtered suspensions of the nasal mucous membranes from
snuffles animals and inoculated them both intranasally and intracere-
brally in young stock rabbits.

Two stock rabbits with typical snuffles were killed by pithing, and the nasal
and sinus mucous membranes were dissected out. The resulting material was
ground with sand and 10 cc. of saline solution, centrifuged lightly to remove
large particles, and the supernatant fluid was passed through a Berkefeld V
candle. The clear filtrate showed no growth on the usual media.

The filtrate, 0.5 cc. into each nostril, was inoculated into each of three young
rabbits, but these failed to show any symptoms.

The experiment was repeated three times, employing different sources for the
snuffles material, but in all cases the results were negative or indecisive.

Five different samples of filtrates were inoculated intracerebrally in doses of
0.25 to 0.35 cc. into eight young rabbits. In no instance did there develop
clinical evidence of snuffles, nor any untoward symptoms.

Thus both the unfiltered and the filtered suspensions of snuffles
material, the unfiltered inoculated intranasally, the filtered, intranasally
and intracerebrally, failed to induce the disease in supposedly normal
stock rabbits.

DISCUSSION AND SUMMARY.

In our experience, covering a large number of rabbits, we have found
that the condition known as snuffles falls into different types, the acute
and fatal, symptomatic of some underlying infection such as septicemia
or pneumonia; and the intermittent, and the chronic. The intermit-
tent and the chronic types considered in this paper are those most
commonly present in laboratory stocks.

Our observations point to a widespread prevalence of the disease
among rabbits kept under laboratory conditions. This statement
might be questioned had the stock we examined been derived from a
single source. But the animals were procured from dealers who
obtain rabbits in New York, Pennsylvania, Ohio, and as far west as
Michigan. The same dealers supply the stock of most of the labora-
tories in the East. Hence we believe that this disease is found
generally prevalent in this part of the country.
We have demonstrated that practically all rabbits with intermittent or chronic snuffles reveal old chronic inflammatory processes of the upper nasal passages associated with thick inspissated pus in one or more sinuses. Moreover, these conditions are also present in about one-tenth of carefully selected, supposedly normal stock rabbits and in one-fourth of a casually selected group, free, during long periods of observation, from any of the symptoms of active snuffles. The peculiar anatomy of the animal's nose which predisposes to the ready formation of enclosed pockets of purulent material may be the cause for the chronicity of upper nasal affections. When the animal's resistance is lowered, the long standing, inflammatory process can flare up into an acute exacerbation, and then show itself as typical snuffles. Various means can effect this: chilling the body, the intravenous injection of foreign proteins such as killed vaccines, or the intranasal inoculation of microorganisms of divers species. Bacteriological examination of the nasal secretions or sinus pus from animals with snuffles and those apparently free of the disease shows the presence in both cases of various microorganisms—Staphylococcus albus, Bacillus bronchisepticus, Bacillus lepisepticus, and others, in order of frequency. Different bacteria may be found in different sinuses in the same animal.

A lack of recognition of these factors has led, we believe, to erroneous conclusions with regard to the inciting agent of the disease. Bacillus lepisepticus and Bacillus bronchisepticus have been declared the incitants of snuffles. Our experiments, in which an attempt was made to induce the disease de novo with these microorganisms, failed. In all cases (with a single exception) in which snuffles followed, there was evidence of an infection which, judging from the condition of the nasal passages and from the cells in the exudates or secretions, had existed before the inoculations were made. Furthermore, the microorganisms recovered from the nasal passages had as a rule no relationship to those in the material inoculated. We attempted also to produce snuffles by inoculating intranasally the unfiltered and filtered suspensions of the ground nasal mucous membranes from typical cases of the disease occurring in stock rabbits. These attempts also failed.
It appears, therefore, that intermittent and chronic snuffles, as it attacks rabbits kept under laboratory conditions, is, as a rule, a sign of an underlying condition—an exacerbation of a chronic inflammatory process in the upper nasal passages, associated with a purulent paranasal sinusitis. The microorganisms recovered are to be looked upon as tending to maintain such conditions but we have still been unable to reproduce typical snuffles with them, employing supposedly normal stock rabbits for the purpose. One may presume that some agent, as yet undetermined, diminishes the resistance of the nasal mucosa, allowing different bacteria to invade and multiply there, thus causing disturbance. In this respect perhaps an analogous condition exists to that which prevails in epidemic influenza and common colds in man.

It is obvious that further work along these lines cannot be properly carried out with rabbits whose antecedent history is unknown. The problem of the incitant of snuffles can best be studied in a breeding stock which is well controlled, one affording an opportunity to observe the animals from an early period of life.

CONCLUSIONS.

A study of snuffles in stock rabbits reveals that this disease is associated with a chronic inflammatory condition of the upper nasal passages together with purulent paranasal sinusitis. The outward signs of snuffles are, as a rule, the expression of an exacerbation of preexisting inflammation in the upper nasal mucosa. While it is conceivable that in early or incipient cases the disease may be uncomplicated and independent of chronic inflammatory processes, we have not been able to observe such cases. Supposedly normal stock rabbits, even those carefully selected and quarantined, exhibit the chronic inflammation just referred to. Such animals cannot therefore be employed for the solution of the problem of the actual incitant, which is, as yet, undetermined.