

BACTERIOLOGY AND CONTROL OF ACUTE INFECTIONS IN LABORATORY ANIMALS.¹

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In July 1910 the writer published an article (1910¹) entitled "A Preliminary Report of the Bacterial Findings in Canine Distemper," in which was described the organism responsible for the disease. Within a few months a complete report (1911²) was given in a paper entitled "Etiology of Canine Distemper." Almost simultaneously with the second report an article (1911³) appeared, by M'Gowan of Edinburgh, in which was described the same organism. This year an article (1913⁴) appeared, by Torrey and Rahe of New York, corroborating the findings of the two previous workers.

It is important to note that the organisms found by these investigators were identical, and that their work was carried on absolutely independently of each other, thus establishing in a very conclusive and decisive manner the etiology of the disease.

Soon after the publication of the article by M'Gowan, an opportunity was afforded the writer to study a similar condition, in epizootic form, among rabbits, guinea-pigs, ferrets, and monkeys. He was able to corroborate the results of M'Gowan, and demonstrate the identity of the causal organism with the one described as the cause of distemper in dogs, and also prove the relationship and specific nature of these infections (1912⁵, 1912⁶, 1913⁷).

The diseases encountered in epizootic form, which constitute the subject of this paper, include those mentioned in previous papers (1911², 1912⁵, 1912⁶), as well as an infection among rabbits due to an organism of the rabbit septicæmia type, and an infection among dogs due to an organism of the colon type.

Although the organism, first named by the writer *B. bronchicanis* (1911²), and later changed by him to *B. bronchisepticus* (1912⁵), was isolated in the large majority of cases from the trachea, bronchi, nasal cavity, lungs, blood, spleen, liver, intestinal tract, and other locations, other micro-organisms, rather closely allied, culturally, have been found, in some cases, in large enough numbers to claim attention. Some of

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these organisms were found contaminating the *B. bronchisepticus*, and others were in pure culture. Those found associated with the *B. bronchisepticus* were undoubtedly secondary invaders, as were also those found alone. In the latter instance, however, the primary infecting agent, the *B. bronchisepticus*, was either overgrown or had disappeared, and the animals had yielded to the secondary infections. Torrey mentions a similar condition among his dogs, and gives this as an explanation as to why the *B. bronchisepticus* is not always found in the later stages of the disease. The writer showed very conclusively in his earlier articles on the subject, that, in order to obtain the specific organism without much difficulty, the case must be taken in the early stages of the disease. M'Gowan (1911⁸) also, in an epidemic among cats due to this same organism, found that the animals died from secondary infections, which, in some cases, had entirely supplanted the primary.

One object of this paper is to describe the various organisms resembling the *B. bronchisepticus*, and some experiments carried out with them, to determine, if possible, the exact status of the *B. bronchisepticus* as regards micro-organisms of similar morphology which are found at times associated with it. This work is the outcome of a discussion of a paper (1913⁷) on the subject of distemper, in which the question was raised as to whether the *B. bronchisepticus* was one of a large group of organisms with slight cultural variations, or a distinct species.

Before considering the experiments in detail, however, it may be well to give, briefly, the symptomatology and bacteriology of the infections, as found by the writer, in laboratory animals.

Infections with B. bronchisepticus.

Dog.—*Symptomatology.*—Cough, diarrhœa, serous, followed by purulent, discharges from the nose and eyes, together with loss of appetite and flesh, are the most pronounced symptoms. The disease may be ushered in with convulsions, especially in the very young, and result in death within a few hours. A pustular skin lesion is found in about 10 to 15 per cent. of cases. Acute symptoms usually last from a few days to two or three weeks, and are followed by death in 60 to 90 per cent. of cases. The case may go on to a complete recovery or to a chronic condition lasting several months, or it may terminate in a condition called "chorea." Incubation period is from five to seven days.

Bacteriology.—In the very early stages the *B. bronchisepticus* may be found in pure culture in the respiratory tract, blood, and often in the abdominal organs, and it may be isolated from the intestinal tract. In later stages the specific micro-organism is found associated with a variety of secondary organisms, especially the *Staphylococcus albus* and *Streptococcus pyogenes*.

Guinea-pig.—*Symptomatology.*—The symptoms first noticed are weakness, diarrhœa, loss of appetite and flesh. When observed in the cage at rest or walking about, the back will be arched and the hindquarters drawn up; this attitude is very characteristic. Death will follow within a few days in

a large majority of pigs affected. Females are more susceptible than males, and the prognosis is invariably fatal in pregnancy. Incubation period is from three to five days.

Bacteriology.—The specific micro-organism is found in the upper respiratory tract in pure culture, and often in the abdominal organs and intestinal canal in association with other organisms. The animal usually dies before secondary organisms become very much in evidence, except in the intestinal canal; wherein it differs from the dog.

Rabbit.—**Symptomatology.**—Loss of appetite and flesh with decreased activity are usually the initial symptoms. Diarrhœa is an invariable symptom, while a discharge from the nose and eyes (purulent very early) is recognised in most cases; wherein it differs from the guinea-pig. Death in the majority of cases is found in from two to ten days, although the disease is not so fatal as with the guinea-pig. Incubation period from five to seven days.

Bacteriology.—In the early stages the *B. bronchisepticus* is usually found in the respiratory tract in pure culture. It may also be found in the blood and abdominal organs. In later stages the specific micro-organism is associated with pyogenic organisms of secondary infections.

Monkey.—**Symptomatology.**—Loss of appetite and flesh with decreased activity are about the first symptoms noticed. Diarrhœa is invariably present and an occasional cough is heard. A discharge from the nose or eyes has not been observed. The disease usually lasts from one to two weeks. The incubation period is about one week.

Bacteriology.—The *B. bronchisepticus* has been isolated in pure culture from the respiratory tract and blood. It has also been found in the abdominal organs and intestinal canal. Some of the cases terminated in a streptococcus septicæmia.

Ferret.—**Symptomatology.**—The symptoms are very similar to those found in the rabbits, including loss of appetite and flesh, diarrhœa and purulent discharge from nose and eyes.

Bacteriology.—*B. bronchisepticus* found in respiratory tract in pure culture in early stages. In later stages it is liable to be overrun with the secondary invaders.

Rabbit Septicæmia.

Symptomatology.—The duration of the disease is, as a rule, but a few hours, so that the symptomatology is not very important. Often a slight discharge may be found at the nostrils, but this is not so profuse nor so purulent as is found in the "snuffles" due to *B. bronchisepticus*. A slight discharge, in fact, seems to be a common symptom of most infections in the rabbit. An infection with the bacillus of rabbit septicæmia seems to be about the most fatal of any of the rabbit diseases.

Bacteriology.—A general invasion of the body with the specific micro-organism.

Infection of Dogs with an Organism of the Colon-para-colon Type.

Symptomatology.—Practically the only symptoms noticeable were a rapid emaciation and diarrhœa, coincident with a loss of appetite resulting in death within a few days.

Bacteriology.—The micro-organism, thought to be the *B. enteritidis*, which was found to be the cause, was isolated in pure culture from the blood and organs. Cultures taken from the trachea and lungs gave no growth. The intestinal canal was not cultured.

DESCRIPTION OF THE SECONDARY ORGANISMS UNDER DISCUSSION,
WITH THE *B. BRONCHISEPTICUS* FOR COMPARISON.

Only those motile, Gram-negative bacilli which resembled the *B. bronchisepticus* by their early growth on agar were retained for study. All cultures were under observation two weeks when the final readings were taken. No attempt has been made to identify these organisms other than to place the organisms of Group I. with the *B. enteritidis* group.

B. bronchisepticus.

Morphology.—Short, narrow. *Agar stroke*.—Moderate, filiform, moist, glistening, translucent. *Bouillon*.—Cloudy with sediment. *Potato*.—Abundant, dark tan. *Litmus milk*.—Marked alkaline. *Glucose agar*.—No gas. *Gelatin*.—No liquefaction.

Group I. (*B. enteritidis*).

No. of strains isolated—17. *Morphology*.—Medium size, broad. *Agar stroke*.—Moderate, lobate, glistening, translucent. *Bouillon*.—Cloudy at first, tendency to clear up later. *Potato*.—Slight, colourless. *Litmus milk*.—Acid, changing to alkaline. *Glucose agar*.—Gas. *Gelatin*.—No liquefaction.

Group II.

No. of strains—2. *Morphology*.—Long, narrow. *Agar stroke*.—Moderate, lobate, glistening. *Bouillon*.—Cloudy first, clears up with sediment. *Potato*.—Abundant, cream. *Litmus milk*.—Marked acid, no coagulation. *Glucose agar*.—Gas. *Gelatin*.—No liquefaction.

Group III.

No. of strains—1. *Morphology*.—Long, narrow, bipolar. *Agar stroke*.—Abundant, spreading, glistening, turning the medium darker. *Bouillon*.—Flocculent at first, clears, with heavy film and heavy sediment. *Potato*.—Slight, colourless. *Litmus milk*.—Colour disappears at first, later acid. *Glucose agar*.—No gas. *Gelatin stab*.—Liquefaction.

Group IV.

No. of strains—1. *Morphology*.—Small. *Agar stroke*.—Moderate, filiform. *Bouillon*.—Clear and viscid sediment. *Potato*.—Moderate, tan. *Litmus milk*.—Slightly alkaline. *Glucose agar*.—No gas. *Gelatin*.—No liquefaction.

Group V.

No. of strains—1. *Morphology*.—Large. *Agar stroke*.—Moderate, echinulate. *Bouillon*.—Cloudy. *Potato*.—Slight, colourless. *Litmus milk*.—Acid coagulation. *Glucose agar*.—Gas. *Gelatin*.—Liquefaction.

Group VI.

No. of strains—3. *Morphology*.—Large. *Agar stroke*.—Moderate, lobate. *Bouillon*.—Cloudy. *Potato*.—Abundant, yellow. *Litmus milk*.—Acid, coagulation. *Glucose agar*.—Gas. *Gelatin*.—No liquefaction.

Group VII.

No. of strains—2. *Morphology*.—Large. *Agar stroke*.—Moderate, lobate. *Bouillon*.—Cloudy. *Potato*.—Abundant, cream. *Litmus milk*.—Slightly acid, changing to alkaline. *Glucose agar*.—No gas. *Gelatin*.—No liquefaction.

TABLE I.

| | Agar Stroke. | | | | Bouillon. | | | Potato. | | | | Litmus Milk. | | | | | Number. | | |
|-----------------------------|--------------|---------|------------|-------------|-----------|--------|-------------|---------|---------|------|-----------|--------------|--------------|-------------------|---|------|---------------|----|--|
| | Filiform. | Lobate. | Spreading. | Echinulate. | Cloudy. | Clear. | Colourless. | Cream. | Yellow. | Tan. | Alkaline. | Acid. | Coagulation. | Acid to Alkaline. | Colour disappears, followed by marked Acid. | Gas. | Liquefaction. | | |
| <i>B. bronchisepticus</i> . | + | + | : | : | + | : | : | + | : | : | + | : | : | + | : | : | : | 87 | |
| Group I . | : | + | : | : | + | : | + | : | : | : | + | : | : | : | : | + | : | 17 | |
| " II. . | : | + | : | : | : | + | + | : | : | : | : | + | : | : | + | + | : | 2 | |
| " III. . | : | : | + | : | : | + | + | : | : | : | : | : | : | : | + | : | : | 1 | |
| " IV. . | + | : | : | : | : | + | + | : | : | : | + | : | : | : | : | : | : | 1 | |
| " V. . | : | + | : | + | + | : | + | : | + | : | : | + | + | : | : | + | : | 1 | |
| " VI. . | : | + | : | : | + | : | + | : | + | : | : | + | + | : | : | + | : | 3 | |
| " VII. . | : | + | : | : | + | : | + | : | : | : | : | + | + | : | : | + | : | 2 | |

While the variations between these organisms were decisive enough to clearly differentiate them, agglutination tests were carried on as controls, to complete the work and corroborate the classifications. It will be seen that in all cases the agglutination tests confirmed, absolutely the cultural work.

Immune sera were obtained from rabbits injected with these various organisms, as well as with various strains of *B. bronchisepticus* obtained from different animals, for the purpose of cross agglutinations, as controls. After first obtaining a small quantity of serum from each rabbit, as a normal control, the animals were given three injections of a fairly heavy suspension of dead organisms in physiological salt solution, intravenously, at intervals of three days, and bled one week after the last injection. The suspensions for the agglutination tests were prepared according to a method described in a previous article (1911²). The tests were allowed to stand in the incubators, and readings were taken at the end of twenty-four hours.

TABLE II.

| Suspension of <i>B. bronchisepticus</i> from | Agglutination Titre of Sera from Rabbits immunised with <i>B. bronchisepticus</i> from | | | | |
|--|--|----------|-------------|----------|---------------------|
| | Rabbit. | Monkey. | Guinea-pig. | Dog. | Intestine of Puppy. |
| Rabbit. | 1 : 3200 | 1 : 6400 | 1 : 1000 | 1 : 3200 | 1 : 3200 |
| Monkey | 1 : 1600 | 1 : 400 | 1 : 1800 | 1 : 2000 | 1 : 1000 |
| Guinea-pig | 1 : 1600 | 1 : 3200 | 1 : 2000 | 1 : 2000 | 1 : 2000 |
| Dog | 1 : 1600 | 1 : 3200 | 1 : 1600 | 1 : 3200 | 1 : 3200 |
| Intestine of puppy . . . | 1 : 1600 | 1 : 3200 | 1 : 1800 | 1 : 3200 | 1 : 3200 |
| Control (normal serum) . | 1 : 10 | 1 : 20 | 1 : 10 | 0 | 0 |
| Ferret | ... | ... | ... | 1 : 2000 | ... |
| Douglass | ... | ... | ... | 1 : 2000 | ... |
| Human | ... | ... | ... | 1 : 3200 | ... |

Experiment 1 (Table II).—Test of several strains of *B. bronchisepticus* isolated from various sources. Cross agglutinations were carried out, except with the strains marked ferret, Douglass, and human.

Experiment 2.—In this experiment (Table III.) suspensions from the organisms resembling *B. bronchisepticus* were tested against a serum immune to strain of *B. bronchisepticus* from dog 36. This serum has always given typical and high agglutination with suspension of *B. bronchisepticus*. It will be seen that the highest titre obtained from any of the secondary organisms was 1 : 400, from Group III., while that from *B. bronchisepticus* was 1 : 3200.

Comparing this with the previous experiment, it will be seen that agglutinations of *B. bronchisepticus* suspensions with their homologous serums are always above 1:1000 and average 1:3200.

TABLE III.—*Agglutination Titre of Serum from a Rabbit.*

(Immunised with *B. bronchisepticus*, No. 36.)

| Suspensions of | | | |
|---------------------------|------------------|--------|--------|
| <i>B. bronchisepticus</i> | | No. 36 | 1:3200 |
| Group I. | Bacillus | " 14 | 0 |
| | " | " 26 | 0 |
| | " | " 34 | 0 |
| | " | " 35 | 0 |
| | " | " 36 | 0 |
| | " | " 45 | 0 |
| Group II. | " | " 38 | 0 |
| Group III. | " | " 52 | 1:400 |
| Group IV. | " | " 54 | ... |
| Group V. | " | " 143 | 1:100 |
| Group VI. | { | " 191 | 1:100 |
| | | " 209 | 1:80 |
| Group VII. | { | " 161 | 0 |
| | | " 162 | 1:10 |

Group I., which was found in a larger number of cases than any of the other secondary organisms (seventeen out of twenty-seven), showed no tendency whatever to agglutinate.

Experiment 3.—This experiment (Table IV.) shows the result of the cross-agglutinations between the organisms of the various groups.

The horizontal rows represent the immune sera. The perpendicular rows represent the suspensions. The figures in italics represent the titre of the suspensions of various bacilli with their homologous serums. The suspensions of *B. bronchisepticus* with their homologous serums gave an agglutination on the average of about 1:3200, while the organisms of the remaining groups appeared to have a tendency to agglutinate in very much higher dilutions, most of them going up as high as 1:10,000. The suspensions of the organism from Group IV. always gave a spontaneous reaction, so that the only means we had of testing this organism was by means of its immune serum against suspensions of organisms from the other groups.

[TABLE

TABLE IV.

| Serum from Rabbit treated with | | | | | | | | | | | |
|-----------------------------------|-----------------------------|-------------|---------------|---------------|------------|-----------|-----------|-----------|------------|-----------|--------|
| Suspensions | <i>E. bronchisepticus</i> . | Group I. | | Group II. | Group III. | Group IV. | Group V. | Group VI. | Group VII. | | |
| | | No. 36 | No. 26 | | | | | | | No. 140 | No. 38 |
| <i>E. bronchisepticus</i> | No. 36 | 1 : 3200 | 1 : 10 | .. | .. | .. | .. | 0 | .. | .. | .. |
| | Bac. No. 12 | Spontaneous | agglutination | 1 : 3200+ | 1 : 40 | 0 | .. | 0 | 0 | .. | .. |
| | " 14 | 0 | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 17 | .. | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 26 | 0 | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 34 | 0 | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 35 | 0 | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 36 | 0 | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 45 | 0 | 1 : 6400 | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 47 | 0 | 1 : 3200+ | 1 : 3200+ | 1 : 100 | 1 : 10 | 0 | 0 | 0 | 0 | 0 |
| | " 63 | .. | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 71 | .. | 1 : 2000 | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 105 | .. | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 140 | .. | Spontaneous | agglutination | .. | .. | .. | .. | .. | .. | .. |
| | " 141 | .. | " | " | .. | .. | .. | .. | .. | .. | .. |
| | " 160 | .. | " | " | .. | .. | .. | .. | .. | .. | .. |
| Group I. . . . | " 177 | .. | 1 : 2000 | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 199 | .. | 1 : 3200+ | .. | .. | .. | .. | .. | .. | .. | .. |
| | " 38 | 0 | 1 : 80 | 1 : 400 | 1 : 10000+ | 1 : 40 | 1 : 100 | 1 : 100 | 1 : 20 | 1 : 80 | .. |
| | " 41 | .. | 1 : 80 | .. | .. | .. | .. | .. | .. | .. | .. |
| Group II. . . . | " 52 | 1 : 400 | 1 : 100 | 1 : 400 | 1 : 40 | 1 : 1000+ | 1 : 3200+ | 1 : 100 | 1 : 100 | 1 : 400 | .. |
| Group III. . . . | " 54 | Spontaneous | agglutination | .. | .. | .. | .. | .. | .. | .. | .. |
| Group IV. . . . | " 143 | 1 : 100 | 1 : 400 | 1 : 400 | 1 : 200 | 1 : 40 | 1 : 10 | 1 : 1000+ | 1 : 400 | 1 : 400 | .. |
| Group V. . . . | " 191 | 1 : 100 | 1 : 200 | 1 : 400 | 1 : 40 | 1 : 100 | 1 : 20 | 1 : 400 | 1 : 1000+ | 1 : 40 | .. |
| Group VI. . . . | " 209 | 1 : 80 | 1 : 200 | .. | .. | .. | .. | .. | .. | .. | .. |
| Group VII. . . . | " 161 | 0 | 0 | 1 : 1000 | 1 : 20 | 1 : 200 | 1 : 40 | 1 : 100 | 1 : 20 | 1 : 1000+ | .. |
| | " 162 | 1 : 10 | .. | .. | .. | .. | .. | .. | .. | .. | .. |

CONTROL OF EPIZOOTICS AMONG LABORATORY ANIMALS.

If infectious diseases among laboratory animals are to be controlled and epizootics prevented, especially where large numbers are housed together, as in breeding stables, strict hygienic measures must be adhered to and sanitary precautions carried out. This includes, wherever applicable, preventive inoculations with specific vaccines.

As regards infections caused by *B. bronchisepticus*, experience has taught us that epizootics can be controlled and a protection afforded the susceptible animals, provided prophylactic injections with vaccines, together with the ordinary sanitary measures, are intelligently and systematically carried out. In the epizootics under discussion, among guinea-pigs and rabbits, due to *B. bronchisepticus*, vaccines were made up with the specific bacillus, 100,000,000 per cubic centimetre. Each animal was injected with its homologous vaccine every third day, starting with 1 c.c. and increasing the dose 1 c.c. at each subsequent injection.

The epizootic, due to the colon-like bacillus, which simulated an acute type of distemper, and might easily have been mistaken for it, was found among a number of young dogs which were being saved for experimental purposes, and had therefore received their regular prophylactic vaccinations against *B. bronchisepticus*. It was thought at first that the dogs were suffering from true distemper, and that the vaccine in this case was not protecting. After a thorough bacteriological examination had been made of every dog that died, it was found that the *B. bronchisepticus* was not present and that another bacillus of a very similar morphology was responsible for the trouble. This bacillus, which was probably the *B. enteritidis*, was found to be extremely virulent, a very small dose, upon subcutaneous inoculation, killing a dog within a day or two with an acute general infection.

This incident showed very strikingly that at least one disease similar to the acute form of distemper may at times appear in epizootic form; and in order to differentiate the condition from distemper a bacteriological examination would be necessary.

The epizootic, due to the bacillus of rabbit septicaemia type, did not respond so readily, in our hands, to prophylactic injection with a specific vaccine. A vaccine made up with this bacillus, 100,000,000 per c.c., given in three injections of increasing doses, offered practically no protection. It was found, experimentally, also, that three doses did not protect rabbits from the M. F. D. of this organism. The results of the experimental as well as the clinical tests convinced us, therefore, that, if we are to protect against the disease, at least a more protracted course of treatment with the prophylactic vaccine would be necessary. This disease was finally controlled only by isolation.

CONCLUSIONS.

From the results of the cultural tests and agglutination experiments, as carried out on the micro-organisms included in this study, it is shown very clearly that the *B. bronchisepticus* is a distinct species. This confirms the previous work of M'Gowan and also the writer, and corroborates the results of Torrey, who says: "We have tested many strains of the bacillus, and in every instance in which there was an exact correspondence with the diagnostic cultural tests there was also a definite agglutination with a single anti-serum." "As regards agglutination, then, there are no sub-varieties of the bacillus, but the same degree of uniformity obtains which is encountered with *Vibrio cholerae* or *B. typhosus*."

It has been found by Torrey, M'Gowan, and the writer, after studying many strains of the bacillus, that the cultural tests are invariable, and, for ordinary routine work, the reactions on litmus milk and potato are characteristic, and that the bacillus may be identified by its behaviour towards these media. The writer has encountered but two organisms which may simulate the *B. bronchisepticus* in its reactions towards these media; namely, the *B. fecalis alkaligenes*, mentioned also by Torrey, and an organism described in this paper as bacillus of Group IV. The *B. fecalis alkaligenes*, however, according to different authorities, does not always produce a characteristic alkaline reaction in litmus milk, while its growth on potato is but slightly raised and not so moist. A culture of this organism received from the American Museum of Natural History, New York, gave, in the hands of the writer, a distinct acid reaction in litmus milk. The organism described in this paper as bacillus of Group IV. might, according to its growth on potato and in litmus milk, be identified as *B. bronchisepticus*, were it not for its growth in bouillon. The bouillon was clear with a stringy sediment, instead of being cloudy. This characteristic clumping was shown very clearly in the agglutination work with this organism. The suspensions of this organism invariably agglutinated spontaneously.

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