RESULTS OF THE INTRATRACHEAL INJECTION OF THE BORDET-GENGOU BACILLUS IN THE MONKEY AND RABBIT

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PLATES 10 AND 11

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Since the discovery of the Bordet-Gengou bacillus in 1906 (1), there have been a number of reports regarding the relationship of this organism to pertussis. The literature has been reviewed so extensively that only the recent work dealing with attempts to produce this disease in apes will be mentioned.

Sauer and Hambrecht (2) report that a paroxysmal cough developed in 5 cebus monkeys inoculated intralaryngeally and in 3 macaques after intranasal instillation. 2 of the macaques developed a lymphocytosis of over 20,000 cells per c. mm. The other macaque and the cebus monkeys with but one exception had a lymphocytosis of over 13,000. Culotta and his associates (3) were unable to obtain either lymphocytosis or cough in 12 *Macacus rhesus* monkeys which were inoculated intratracheally but were successful with 2 cebus monkeys. Sauer and Hambrecht (4) reported in detail the anatomical findings in a *rhesus* and a ringtail monkey, which were killed at the height of the experimentally induced disease and from which the Bordet-Gengou bacillus was recovered. Sections through the lungs of the *rhesus* monkey showed a number of pertussis organisms on the cilia and some of the bronchioles were blocked with mucus and cells. The alveoli and the interstitial tissue were in some areas filled with round cells, leucocytes, fibrin, erythrocytes, and pertussis-like organisms. Sections through the lungs of the ringtail monkey showed a similar but less marked picture.

Rich and his associates (5) by intratracheal injection of the Bordet-Gengou organisms were able to produce a lymphocytosis and a paroxysmal cough in chimpanzees but no anatomical studies were made.

From the work described above it is evident that the Bordet-Gengou bacillus can produce in monkeys a syndrome similar to that

seen in man. We have shown in a previous publication that this organism could produce an interstitial mononuclear pneumonia in the rabbit, and we thought it worth while to study in more detail the clinical and anatomical changes which can be produced in the monkey and also to extend our previous work with the rabbit (6).

Methods

Animals.—8 male and 3 female monkeys of the erythrocebus variety were used. The precise age of these animals could not be ascertained but from their behavior, weight, and white cell count we judged that we had 1 adult male monkey and 7 young ones. The female monkeys were apparently almost full grown.

Full grown rabbits weighing more than 2 kilos and shown by a method previously described (6) to be free from *Bacterium lepisepticum* and *Bacillus bronchisepticus* were used. The technique of inoculation and necropsy has been described in a previous paper (6).

Blood Counts.—The white blood counts were made just before the regular feeding time. The blood was drawn from an ear vein. In order to minimize the possibility of error the same pipettes were used for each monkey throughout the experiment. The differential formulae were computed from the study of 1,000 leucocytes. Peroxidase stains also were made and counted but these agreed in every instance with the results obtained with the Wilson stain.

As both the monkey and the rabbit are noted for the wide variations in their white cell counts, it was thought essential to determine the upper limit of the normal variation of these counts. Therefore, total and differential counts of 4 monkeys were made over a period of 10 weeks. Although the total counts were found to be exceedingly variable, none was found in which the lymphocytes exceeded 13,000 cells per c. mm. Scarborough (7), in his summary of the literature, found this to be true. We had available over 300 leucocyte counts and differential formulae for normal rabbits. The upper limit of the lymphocytes in these animals was 15,500 cells.

Diet.—The monkeys were kept in individual cages and fed once a day on a diet composed of bread, milk, bananas, and cod liver oil.

Cultures.—A number of strains of the Bordet-Gengou bacillus[1] were grown for 48 hours on the Bordet-Gengou medium to which 20 per cent human blood was added. The organisms were washed from the slants in saline and then injected intratracheally into rabbits. In Experiment 1 with monkeys 1, 2, 3, and 4 a strain was used which produced a good interstitial mononuclear pneumonia in rabbits. In Experiment 2 a mixture of 5 strains was employed. All of these strains both individually and when mixed produce an interstitial mononu-

[1] These strains were obtained through the courtesy of Dr. W. A. Jamieson of Eli Lilly and Company.

clear pneumonia in rabbits. In Experiment 3, the organisms recovered from monkey 6 were used. The avirulent organisms which were used in certain of the monkeys and rabbits were obtained from Dr. J. A. Toomey. These were grown on the solid veal brain media described by him (8).

Inoculation.—The monkeys were lightly anesthetized with ether. The skin over the trachea was painted with tincture of iodine. A needle was then inserted through the skin into the trachea and the inoculum injected slowly. The animals were kept under the effect of ether for a few minutes to prevent their coughing up the material.

Necropsy.—Monkeys 1, 2, 3, and 4 were killed with chloroform and were necropsied at once. Monkeys 5, 6, 7, and 8 died and were necropsied at once, or within 3 hours after death. Since the use of chloroform in monkeys 1, 2, 3, and 4 might have resulted in the bacterial contamination of the lungs, the remaining monkeys, 9, 10, and 11, were killed by a sharp blow on the head. At necropsy the thorax was opened aseptically and a portion of the lung from the region of the lesion, if present, was taken for culture. This piece of lung was divided into 4 parts which were cultured aerobically and anaerobically in beef infusion broth with a pH of 7.4, on blood agar plates and on the Bordet-Gengou plates. In addition to these cultures, a long platinum loop was inserted deep into the bronchi and the recovered material streaked on blood agar and Bordet-Gengou media.

The lungs were inflated with air and fixed in Zenker's solution. Cross sections through the hilus were taken from each lung. After being embedded in paraffin, these were stained with hematoxylin and eosin, the MacCallum, and the Brown and Breen methods for bacteria, and for iron pigment.

Nasal Cultures.—Deep nasal swabs were cultured before the onset of the experiment for *Bacillus bronchisepticus* and *Bacterium lepisepticum* and none was found. After injection deep nasal swabs were taken daily. These were cultured on the Bordet-Gengou media.

EXPERIMENTAL

This experiment was designed to verify the observations of Sauer and Hambrecht (2) and Culotta and his associates (3), that the Bordet-Gengou organism would produce a pertussis-like syndrome in monkeys, and to study the anatomical changes in these animals. The clinical course and changes in the lungs will be outlined briefly.

Experiment 1.—4 monkeys were used in this experiment.

Monkey 1, weight 2,150 gm., was given 1 cc. of a suspension containing a 48 hour growth from 4 Bordet-Gengou slants. The lymphocytes in this animal never went above 12,000 cells per c. mm. This monkey was killed 14 days after inoculation with the Bordet-Gengou bacillus.

Necropsy.—Gross: The lungs were deeply pigmented and no mucoid material was found in the bronchi.

Microscopic: In many places the alveoli were filled with macrophages which contained hemosiderin. There was no marked increase in the number of cells in the interstitial tissue elsewhere.

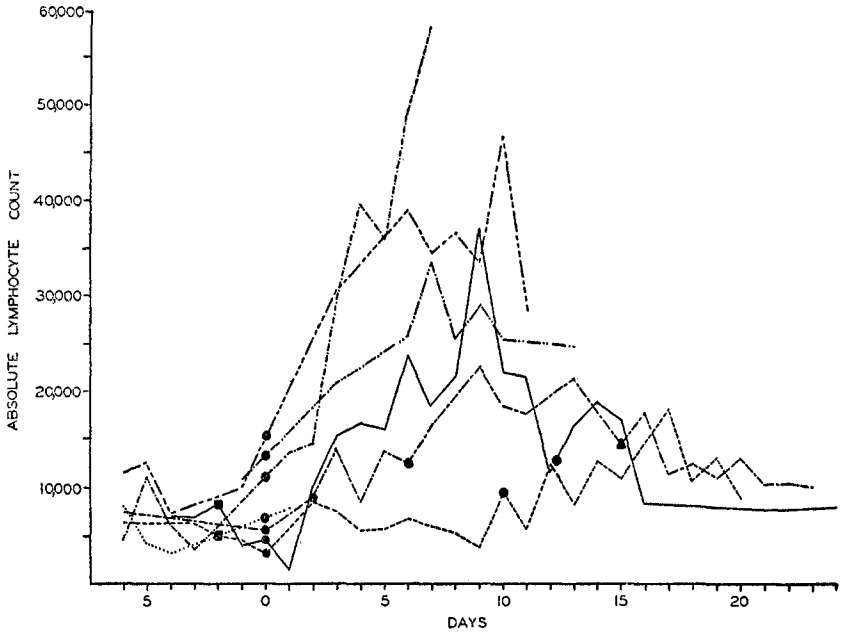

CHART 1

CHARTS 1 and 2.

Monkey 2	Total leucocytes and lymphocytes	— — — —
Monkey 3	Total leucocytes and lymphocytes	— · — ·
Monkey 5	Total leucocytes and lymphocytes	· · · · · · · ·
Monkey 6	Total leucocytes and lymphocytes	— · — · —
Monkey 9	Total leucocytes and lymphocytes	————
Monkey 10	Total leucocytes and lymphocytes	— — — —
Monkey 11	Total leucocytes and lymphocytes	----------

Virulent Bordet-Gengou bacilli injected ●
Avirulent Bordet-Gengou bacilli injected ▲
Staphylococcus toxin injected ■

Monkey 9 received one more injection of avirulent Bordet-Gengou bacilli which is not shown in the charts. This caused no change in either the leucocytes or lymphocytes.

Monkey 2, weight 900 gm., was given material from 2 Bordet-Gengou slants. The increase of lymphocytes was so slight that this animal was reinoculated with the material from 4 Bordet-Gengou slants. This resulted in a definite lymphocytosis, as shown in Chart 1. It was killed 14 days after the second inoculation.

Necropsy.—Gross: There was a small area of consolidation near the hilus. The lower lobes of both lungs were congested. The bronchi contained a tenacious yellow mucoid material.

Microscopic: In the lung there was an area, near the hilus, measuring about 10 x 4 mm. containing foci of necrosis. The tissue around these areas was filled

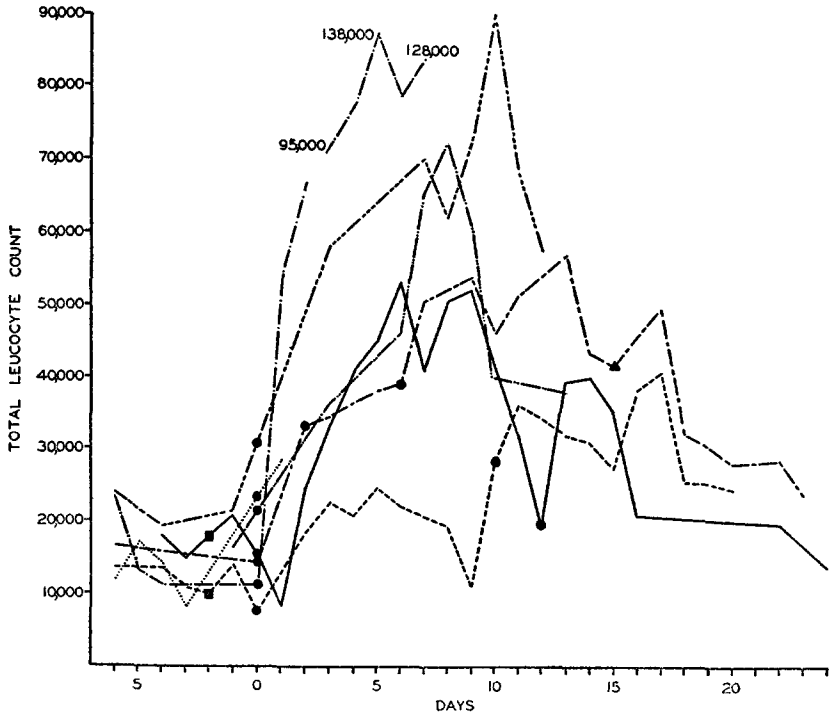

CHART 2

with mononuclear cells. The remainder of the lung tissue showed thickening of the interstitial tissue and some small focal accumulations of mononuclear cells. No bacteria were seen in the sections.

Monkeys 3 and 4, weight 1,300 and 1,350 gm., were both given material from 2 Bordet-Gengou slants and the results were essentially alike. Both monkeys were less active the day after injection and later were slightly sick. There was a definite lymphocytosis in both animals. The changes in monkey 3 are shown in Charts 1 and 2. The changes in monkey 4 were of the same magnitude but were omitted for the sake of brevity. They were killed 14 days after inoculation.

Necropsy.—Gross: The lungs were slightly congested and the bronchi contained a tenacious yellow mucoid material. Both lungs were easily inflated.

Microscopic: Throughout the lungs there was a definite increase in the number of mononuclear elements in the interstitial tissue. In addition to this there were focal accumulations of mononuclear cells, many of which were macrophages. They did not contain hemosiderin. The perivascular lymphatics also contained a number of cells and showed a slight increase of fibrous tissue around the bronchi. Figs. 3 and 4 show the characteristic picture seen in monkey 3.

Bacteriologic Report.—The Friedländer's bacillus, *B. coli* and *B. fecalis alkaligenes* were recovered from the lungs and bronchi of monkeys 1, 2, 3, and 4.

This experiment was done to determine the effect of larger amounts of the organism.

Experiment 2.—4 monkeys were to be used in this experiment. 2 of these died presumably of poison before the experiment was started but are included as controls.

Monkey 5, weight 1,000 gm., was given material from 8 Bordet-Gengou slants in 3 cc. of saline at 3 o'clock in the afternoon. The next morning it was inactive and would not eat. In the afternoon, it was lying down in the cage, vomited, and at times had a non-paroxysmal cough. At 10 o'clock the same night it was dehydrated from vomiting. 35 cc. of Locke's solution was given subcutaneously. The animal died a short time later (31 hours after injection) and was necropsied immediately. Charts 1 and 2 show the changes in the peripheral blood.

Necropsy.—Gross: At necropsy both pleural cavities were filled with cloudy fluid. The bronchi contained a mucoid material. The lungs were collapsed and red. Both lungs were easily inflated. A few round worms were found in the stomach.

Microscopic: A large proportion of the alveoli were filled with polymorphonuclear leucocytes and fibrin. The bronchi as a rule were free from exudate. A few, however, contained some fibrin. The remaining alveoli were filled with an amorphous granular material. A few swollen Gram-negative rods were found both in the alveoli and in the bronchi but cultures of this lung were sterile. The perivascular lymphatics contained a large amount of fluid but few cells.

Monkey 6, weight 1,100 gm., was inoculated with the same amount of material as monkey 5. The following day it was slightly lethargic but shortly regained its vitality. The only symptoms noted until the 6th day after inoculation were slight decrease in activity and loss of appetite. On the 6th day the animal began to vomit and had a slight wheeze and cough. Death occurred early on the morning of the 8th day after inoculation. The changes in the lymphocyte count are shown in Chart 1.

Necropsy.—Gross: The pleural cavities were filled with an opalescent fluid. The lungs could not be inflated and had firm lesions which extended from the hilus to the pleura. The bronchi contained a tenacious yellow mucoid material. Nothing more of interest was seen.

Microscopic: The alveoli throughout the sections contained a granular amorphous material and a few contained fibrin. A few small focal areas of necrosis were seen. The dominant feature, however, was the presence of large numbers of mononuclear cells, both in the alveoli and in the interstitial tissue. A few of these cells were lymphocytes. The majority of the cells, however, were either macrophages or monocytes. A few of the macrophages contained a small amount of hemosiderin. Red blood cells were seen in some alveoli, a few of which had been phagocytized. In addition to these elements there were some cells which were probably epithelial cells and some polymorphonuclear leucocytes. These were present in the interstitial tissue in the alveoli and in the bronchial epithelium. The perivascular lymphatics contained a number of mononuclear elements. No cells were seen in the bronchi but there was in places a considerable amount of amorphous debris. The changes in the lung are shown in Figs. 1 and 2. Embedded in the cilia of the smaller bronchi were found scattered small Gram-negative coccobacilli. An occasional Gram-positive coccus was seen. On the cilia of the larger bronchi there were areas which contained numerous Gram-negative bacilli, some of which were small coccobacilli. Most of the organisms were larger (2–3 μ and occasionally 4 μ by 0.8 to 1 μ) and stained irregularly, resembling the swollen degenerate forms seen in old cultures of bacteria. The streaked plate cultures showed innumerable colonies of the Bordet-Gengou bacilli and a few colonies of colon bacilli. Although it was impossible to determine whether or not these structures represented degenerate colon or Bordet-Gengou bacilli, the predominance of colonies of the latter on culture of this material added support to the view that these large bacterial forms were Bordet-Gengou bacilli.

Monkeys 7 and 8 are included as controls. After having been kept a month these animals began refusing their food. The next day they were quite ill and vomiting. Death occurred within 24 hours after the onset of the symptoms. These animals had been observed over a period of 8 weeks with blood counts twice weekly.

Necropsy.—Gross: The lungs inflated well and showed no changes. The liver was quite yellow. No other abnormalities were seen.

Microscopic: The alveolar walls were quite thin and no lining epithelial cells were seen. The bronchi and bronchioles were surrounded by a small amount of lymphoid tissue. The bronchial epithelium was well preserved and a moderate number of goblet cells were seen. The perivascular lymphatics were not dilated and contained no pus. The livers of both animals were almost completely necrotic. The convoluted tubules showed some necroses. It was thought that the animals were accidentally poisoned.

This experiment was designed to see if by damaging the lung we could not increase its susceptibility to the Bordet-Gengou bacillus. This was thought possible since pertussis is considered by some as being the result of a virus and the Bordet-Gengou bacillus. No virus

being available, it was decided to use staphylococcus toxin and multiple injections of the Bordet-Gengou bacilli as these had in earlier publications by us (6) been shown to cause anatomical changes similar to those caused by many viruses.

Experiment 3.—3 monkeys were used in this experiment.

Monkey 9, weight 1,800 gm., was given intratracheally 0.2 cc. of staphylococcus toxin. 2 days later the bacilli obtained from 4 Bordet-Gengou slants in 2 cc. of saline were injected intratracheally. This was repeated 12 days later and 17 days later the material from 6 slants of the avirulent organisms was injected. The animal was killed 11 days after the last injection. During the entire course of the experiment no changes were noticed in the monkey's behavior. The changes in the blood counts are shown in Charts 1 and 2.

Necropsy.—Gross: The lungs and other viscera showed no lesions.

Microscopic: The changes were essentially like those described for monkey 10.

Monkey 10, weight 1,800 gm., was inoculated intratracheally with the bacteria from 4 Bordet-Gengou slants in 2 cc. of saline. This same dose was repeated 2 and 4 days later. 9 days after this the material from 8 slants of the avirulent organism were given. The animal was killed 8 days after the last injection. The clinical course and the peripheral blood changes were similar to those of monkey 9, as is shown in Charts 1 and 2.

Necropsy.—Gross: The lungs and other viscera showed no changes.

Microscopic: There was some thickening of the interstitial tissue and a few focal areas where the alveoli were filled with mononuclear cells.

Bacteriological Report: The lungs and bronchi were sterile.

Monkey 11, weight 1,700 gm., was given 0.2 cc. of staphylococcus toxin. 2 days later the animal was given the bacteria from 12 Bordet-Gengou slants and 10 days after this the bacteria from 12 Bordet-Gengou slants. The monkey was killed on the 10th day after the last injection. There were no changes in the monkey's behavior. The blood changes are shown in Charts 1 and 2.

Necropsy.—Gross: No lesions were seen in either the lung or the other viscera.

Microscopic: The lung changes are essentially those seen in monkey 10.

Bacteriological Report: 25 colonies of the Bordet-Gengou bacilli were obtained. No other organisms grew out on the various culture media.

Summary of Results of the Experiments in the Monkey.—The intratracheal inoculation of cultures of Bordet-Gengou bacillus in the virulent phase caused a significant lymphocytosis in 6 out of 9 monkeys and an interstitial mononuclear pneumonia in 8 out of 9 instances. This pneumonia is microscopically composed of a large number of mononuclear cells which are in the alveoli and the interstitial tissue. These mononuclear cells are predominantly monocytes, macrophages,

and epithelial cells. There are, however, some lymphocytes and polymorphonuclear cells. When bacilli resembling the Bordet-Gengou bacilli are seen in the sections they are limited almost entirely to the cilia of the bronchi and bronchioles.

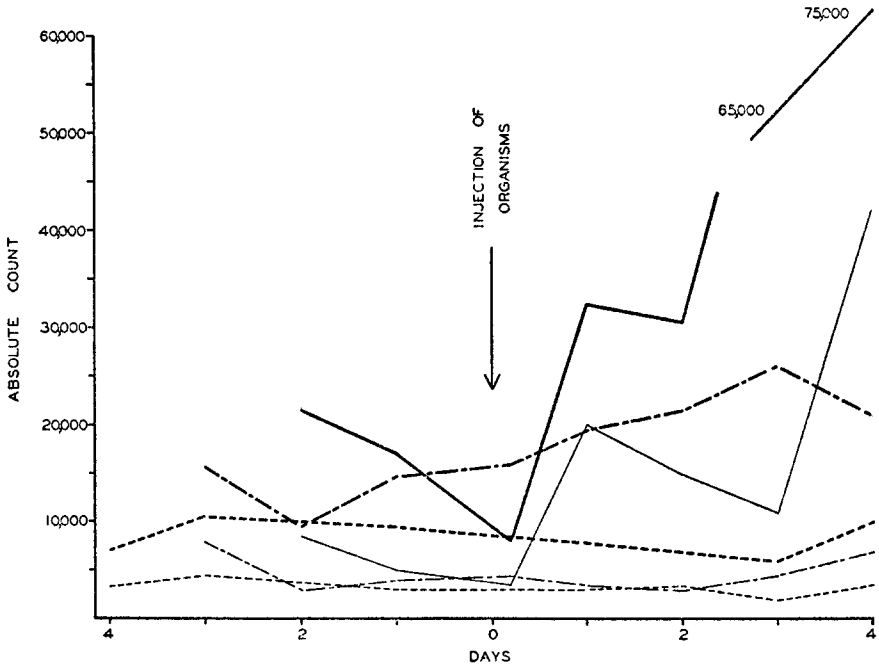

CHART 3

Rabbit receiving virulent Bordet-Gengou bacilli
Leucocytes ——————
Lymphocytes ——————
Rabbit receiving avirulent Bordet-Gengou bacilli
Leucocytes — - — - —
Lymphocytes — - — - —
Rabbit receiving Friedländer's bacilli
Leucocytes - - - - - - -
Lymphocytes ----------

The following experiment was designed to see the effect of the Bordet-Gengou bacillus on the lymphocytes of rabbits. The animals all showed similar lesions to those described previously (6), therefore the morbid anatomical changes will not be described.

Experiment 4.—17 rabbits were inoculated intratracheally with virulent Bordet-Gengou bacilli. All of these animals showed a characteristic lymphocytosis, a typical example of which is shown in Chart 3.

This experiment was designed to show that the organisms other than the Bordet-Gengou bacillus found in the lungs at necropsy played no part in either the lymphocytosis or the interstitial mononuclear pneumonia.

Experiment 5.—6 rabbits were used in this experiment. 2 rabbits were injected with the material from 1 and 2 agar slants of the *B. coli*, 2 with *B. fecalis alkaligenes*, and 2 with Friedländer's bacillus. The lungs of all these rabbits showed extensive necrosis and polymorphonuclear reaction at necropsy and all a depression of the lymphocytes and an increase in the polymorphonuclear leucocytes as illustrated in Chart 3.

This experiment was designed to study the effect of the avirulent organism.

Experiment 6.—6 rabbits were given intratracheally various amounts of these organisms and 2 rabbits were inoculated with similar material heated for an hour at 60°C. The blood picture is shown in Chart 3.

Necropsy.—Gross: Most of the animals showed small lesions near the hilus. The microscopic preparations were similar to those seen when the more virulent cultures were used. The lesions, however, were less extensive. The characteristic lung picture is shown in Figs. 5 and 6. The heated organisms produced lesions similar in every respect to those produced by the unheated ones.

DISCUSSION

These experiments prove that the virulent phase of the Bordet-Gengou bacillus induces a lymphocytosis and an interstitial mononuclear pneumonia in the monkey and the rabbit. The lymphocytosis was shown to be significant; for, although both the monkey and the rabbit are subject to extensive variations in their white counts, these variations are much smaller than the increase produced by intratracheal injection of the Bordet-Gengou bacillus. The interstitial mononuclear pneumonia was present in varying degrees but always had the same characteristics. This pneumonia probably was the result of a toxic material liberated from the Bordet-Gengou bacillus. This is substantiated by the fact that in most instances no organisms were found and in the two instances in which the organisms were

present that they were limited to the cilia of the bronchi and bronchioles and were not found in the alveoli. The other organisms which were cultured from some of the monkeys were shown by experiment to play little if any part either in the morphological change or in the lymphocytosis and were probably only terminal contaminants. The possibility that the lung changes were the result of foreign material and not the toxin from the Bordet-Gengou bacillus was clearly ruled out in a previous publication (6). In these experiments, however, we found that under certain conditions living and heat killed cultures of avirulent Bordet-Gengou bacillus could produce a material, which by acting merely as a foreign body, caused a lesion in the lung similar to that produced by the toxic material of the virulent Bordet-Gengou bacillus. In this case, however, the lesion in the lung was not accompanied by a lymphocytosis and the organisms themselves were dead. This condition also was caused by Bordet-Gengou bacilli which had become completely avirulent. Toomey (8) has shown that these organisms can be recovered from the terminal stages of pertussis in man and that they have the ability to produce quantities of mucoid sticky material in culture.

That the Bordet-Gengou bacilli failed except in 2 instances to multiply in the lungs of the monkeys whereas they are found in large numbers in human pertussis was attributed to the higher susceptibility of man. This susceptibility might be explained by the theory that the spontaneous disease in man was the result of a virus-bacterium complex in which infection with the Bordet-Gengou bacillus was preceded by virus infection which sufficiently changed conditions in the lung to allow the bacteria to gain a foothold and multiply. Since we had shown (6) that staphylococcus toxin and the toxic material from the Bordet-Gengou bacillus could produce changes in the lung similar to those caused by many viruses, it was thought that we could damage the lung with these substances so that the Bordet-Gengou bacillus could gain a foothold. Hence several monkeys were given staphylococcus toxin and then a few days later the Bordet-Gengou bacillus. Other monkeys were given multiple injections of the Bordet-Gengou bacillus at intervals of several days. None of these procedures resulted in the organisms' multiplying in the lungs.

These experiments demonstrate the difficulty of producing pertussis in the monkey. This difficulty may be due to a higher resistance of the monkey to infection with the Bordet-Gengou bacillus or, in spite of our failure to obtain better results when the lung was damaged by toxins, to the possibility that a virus infection precedes the infection with the Bordet-Gengou bacillus.

Although we cannot say what the conditions are which make it possible for this organism to take hold, we believe that the following is a reasonable hypothesis for the development of the disease after the Bordet-Gengou bacillus gains a foothold and multiplies. In this multiplication it releases a toxic material which results in the lymphocytosis and the interstitial mononuclear pneumonia. At the height of the lymphocytosis some of the organisms, having become acclimatized to the host, become the avirulent form producing the sticky mucoid material referred to above. This material can also cause an increase in the amount of interstitial mononuclear pneumonia. This is essentially in agreement with the theory expressed by Toomey (8) in his study of the clinical course of the disease.

The cause of the paroxysmal cough has not yet been satisfactorily explained, but it seems likely since the Bordet-Gengou organisms apparently multiply best on the cilia of the bronchi and bronchioles that they must act as an irritant to cause some of the cough. The production of the mucoid material by the avirulent bacilli may also play a part in causing the cough. McCordock (9) has recently suggested that the cough is the result of damage to the sympathetic ganglion. We have not yet been able to find any confirmation of this possibility.

SUMMARY

Experiments are reported which show that the virulent Bordet-Gengou bacillus can produce a significant lymphocytosis and an interstitial mononuclear pneumonia in both the monkey and the rabbit. Both of these reactions occur apparently as the result of a toxic material formed *in vivo* from the Bordet-Gengou bacillus and are not dependent on the multiplication of the organism itself.

It was also shown that the strictly avirulent form could also cause an interstitial mononuclear pneumonia but no lymphocytosis. This

interstitial mononuclear pneumonia was thought to be the result of the foreign substance produced by the organism when it was in this stage. This was substantiated by the fact that this lesion could be produced both by living and dead organisms.

Since this paper was sent to press, Gallavan and Goodpasture (10) have called attention to a lesion in the epithelium of the bronchi and bronchioles which they have seen both in children dying of pertussis and in the chicken embryo infected with the Bordet-Gengou bacillus. This change consists of a necrosis and cellular infiltration of the epithelium of the bronchi and bronchioles. Further studies of the lungs reported in this paper show this lesion to be present at times in both the monkeys and the rabbits which received the virulent Bordet-Gengou bacilli. This lesion was particularly noted in monkey 6.

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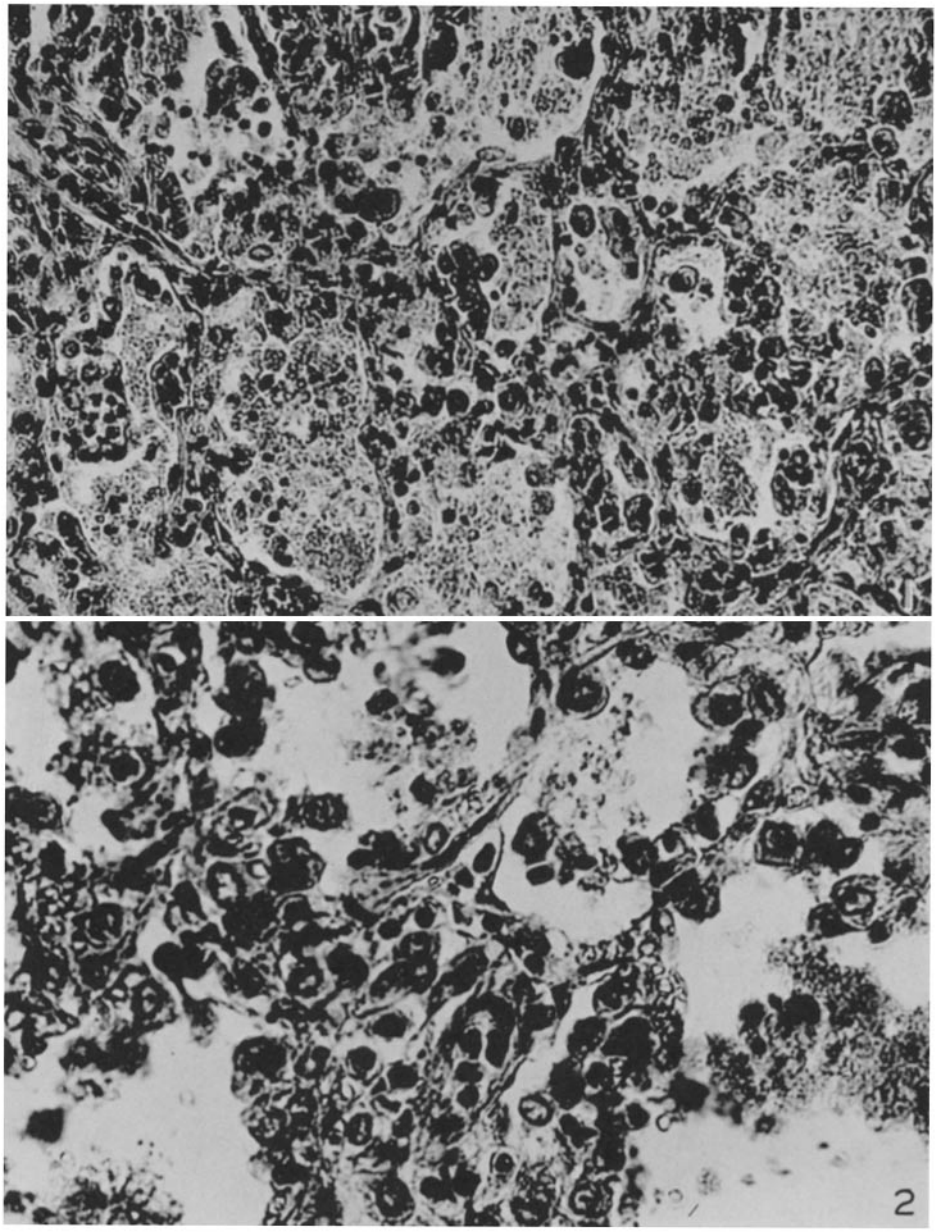
EXPLANATION OF PLATES

PLATE 10

FIG. 1. Section from the lungs of monkey 6 which died 6 days after inoculation with virulent Bordet-Gengou bacilli, showing the characteristic interstitial mononuclear pneumonia. ×300.

FIG. 2. Same as Fig. 1, but showing better the mononuclear nature of the cells. ×660.



(Sprunt *et al.*: Pertussis)

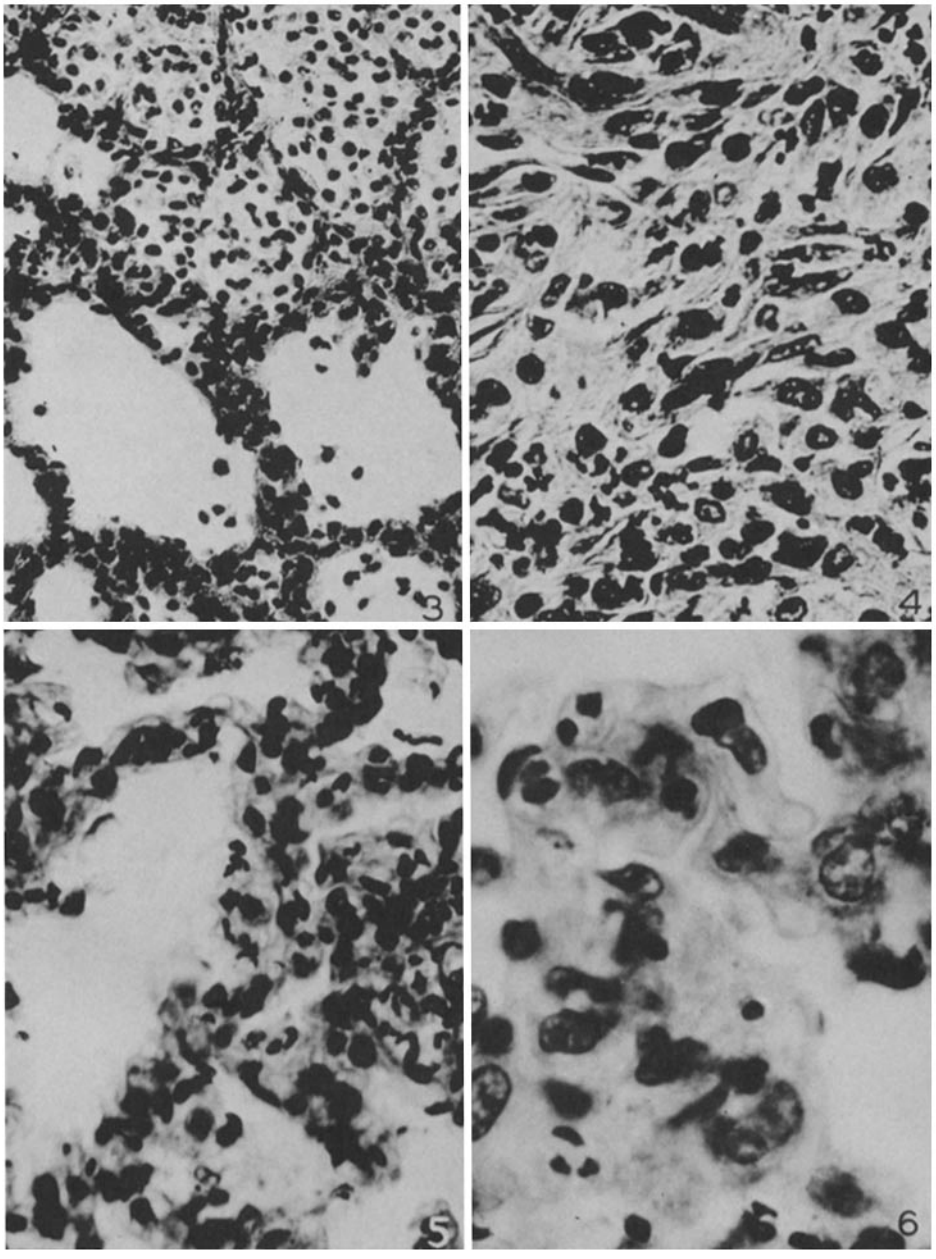
PLATE 11

FIG. 3. Section from the lung of monkey 3 which was killed 14 days after inoculation with virulent Bordet-Gengou bacilli. Note here the dense accumulation of mononuclear cells. × 300.

FIG. 4. Same as Fig. 3 but showing cell types better. × 660.

FIG. 5. Section from rabbit's lung which had received avirulent Bordet-Gengou bacilli and was killed 5 days after injection. Note similarity of reaction to above pictures. × 300.

FIG. 6. Same as Fig. 5, but showing cell detail better. × 660.



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