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PERTUSSIS: THE HISTOLOGICAL LESION IN THE RESPIRATORY TRACT.*

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Introduction. — Microscopic study of the trachea and lungs from three patients who died of whooping cough at the South Department of the Boston City Hospital shows a lesion which involves the ciliated epithelium lining the trachea and bronchi. The lesion is apparently peculiar to this disease and offers, perhaps, a mechanical basis as the cause of the characteristic symptoms. It is due to the presence of great numbers of minute bacilli between the cilia of the cells.

Material available. — The number of cases available for investigation has been very small, owing to the infrequency of death from uncomplicated whooping cough early in the disease. The tissues studied consisted of portions of the trachea and lungs obtained at two recent post-mortem examinations and of small pieces of lung from an autopsy done fifteen years ago. No nasal mucous membrane was preserved in any instance. More careful study of the distribution of the histological lesion throughout the respiratory tract is unquestionably desirable, but there is no knowing when tissue for such a study will be obtained. Therefore, it seems desirable to put on record the present incomplete observations.

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Lesion. — The first of the two recent cases is the more acute. Symptoms had existed for fifteen days or more. Microscopic examination shows large numbers of minute bacteria between the cilia of many of the cells lining the trachea. The cilia of single cells or of small or large groups of them may be thus affected. The microörganisms usually extend to the base of the cilia, but may reach only part way. They frequently cause a lateral spreading or mushrooming of the cilia covering a single cell. In many places the cilia are reduced to short stubs or are entirely wanting. Even these stubs of cilia usually have numerous bacteria packed between them. The long axis of each organism tends to coincide with the direction of the cilia.

The second of the two recent cases was of about forty-two days duration. The cilia lining many of the cells of the trachea have to a large extent disappeared. In places only stubs of them remain. Bacteria are much less numerous than in the first case, but occupy the same position between the cilia even when only stubs of them persist. In one duct running from the trachea to a mucous gland many of the epithelial cells are ciliated. Between the cilia of some of these cells organisms similar in appearance to those in the trachea are present in small numbers.

Careful examination of sections of the lungs from these two cases failed to show any bacteria between the cilia of the cells lining the bronchi and bronchioles. In the lungs, however, of the case autopsied fifteen years ago, in which the symptoms had lasted for about sixteen days, the cells lining these structures in the sections from certain areas show masses of minute bacteria between the cilia. The organisms are, as a rule, fairly uniformly distributed on the surface of all the cells lining the bronchi and bronchioles affected, but other bronchi, sometimes in the same sections, show none at all. Evidently the lesion is not evenly and uniformly distributed throughout the lungs.

Masses of bacteria similar in size and appearance to those between the cilia were found in places in the secretion in the trachea and bronchi. In the trachea they were associated

with cocci of larger size, but in the bronchi they seemed to exist in pure culture. Occasionally they were present in numbers in the cytoplasm of polymorphonuclear leucocytes.

Microörganism. — The bacteria found between the cilia of the cells lining the trachea and bronchi are very minute and stain but lightly by ordinary methods. It is probably on this account that they seem to have been overlooked in the past. The following procedure was found the best for bringing them out distinctly in Zenker-fixed tissues:

Stain paraffin sections by the usual eosin-methylene blue method, but be sure to have the stain with methylene blue intense. Dehydrate quickly without differentiation in absolute alcohol. Clear in xylol and mount in xylol colophonium or balsam. Then differentiate in direct sunlight. This step may require one to many hours according to the intensity of the original stain. Decolorization should be stopped at the stage when the differentiation is sharp and the bacteria are still deeply stained.

The microörganism occurring chiefly between the cilia of the epithelium, but also to some extent in the secretion, is a minute ovoid bacillus. Its center stains less deeply than its ends. It is Gram negative.

The organism suggests strongly the bacillus discovered in 1900 by Bordet and Gengou [1] in the sputum from cases of whooping cough and obtained by them in pure culture in 1906.

This bacillus of Bordet and Gengou is fairly generally accepted by bacteriologists at the present day as the cause of whooping cough, for the following reasons: It is found only in cases of whooping cough and is always present in the earlier stages of the disease. The patient's blood produces an antibody which is specific for this organism as can be demonstrated by the complement-fixation test (the so-called Bordet-Gengou reaction).

Klimenko [2] has confirmed the work of Bordet and Gengou in regard to the cultural peculiarities of Bacillus pertussis

and its biological reaction with the blood of whooping cough patients. In addition he has produced with this organism an infection of the respiratory tract in monkeys and puppies with symptoms more or less closely resembling those of whooping cough, although without the peculiar whoop, and has obtained the organism again from the trachea and lungs. He was also able to demonstrate the complement-fixation test with the blood of these animals.

Reaction. — The injury caused by the bacilli located between the cilia of the cells lining the trachea and bronchi is slight. The toxin secreted by them must be mild. No necrosis of the cells is produced. At most there occurs a gradual destruction of the cilia and this is doubtful. It is an artefact very easily produced by rough handling post-mortem. Future study must decide this point. In the bronchi of the lung where the cells were perfectly protected no such denuding of the ciliated epithelium had occurred; but this might be due to the lesion in the lung being early.

The reaction on the part of the tissues to the bacilli is moderate. The production of mucus does not seem to be increased. There is, however, a slight to moderate inflammatory exudation evidenced by the migration of polymorphonuclear leucocytes in varying numbers between the epithelial cells lining the trachea and bronchi to reach the lumina of these structures. Occasionally endothelial leucocytes are also present and are sometimes phagocytic for the other leucocytes. The submucosa shows a moderate infiltration with lymphocytes, including plasma cells.

The action of the bacilli in the respiratory tract would seem to be largely mechanical. By their presence in such large numbers, dozens to a hundred or more between the cilia of a single cell, they must interfere seriously with the normal ciliary action and thus with the removal of secretion and of inhaled particles in consequence of which the lungs must be more exposed to infection by inhalation than under ordinary circumstances.

At the same time, the production of a mild toxin and its absorption are shown in several ways:

1. By the exudation of leucocytes into the lumen of the trachea and bronchi from the blood vessels lying outside of them.

2. By certain changes which take place in the lymph nodules of the spleen, lymph nodes, and gastro-intestinal tract. These changes are mild in character but similar to those occurring in diphtheria, scarlet fever, and certain other infectious diseases, namely, proliferation of endothelial cells in the centers of the lymph nodules and phagocytosis of the adjoining lymphocytes. Fibrin is sometimes formed in the same location. The explanation of this lesion probably is that the endothelial cells proliferate and produce an antitoxin to counteract a toxin brought there by the circulation and in the process use the surrounding lymphocytes as nutritive material.

3. By the production of the well-recognized lymphocytosis of whooping cough, probably also as a result of the reaction to a toxin derived from the bacilli.

4. By the production of an antibody which is present in the blood and acts specifically toward the Bordet-Gengou bacillus.

Bronchopneumonia.—The bronchopneumonia which sometimes develops in fatal cases of whooping cough is perhaps a complication due to other organisms. In the first case, containing many foci of atelectasis, where endothelial and polymorphonuclear leucocytes were present in small numbers in the alveoli, no organisms of any kind could be demonstrated. In the second case, with evident bronchopneumonia, the exudation was more active, polymorphonuclear leucocytes were numerous, and in some of them a few flattened cocci in pairs were present. No organisms similar to those infesting the ciliated epithelium could be found. In the third case, with numerous bacilli present between the cilia of the epithelium lining the bronchioles, no exudation was present in the alveoli.

Results. — The observations recorded here show that a definite relation exists between the causal agent in whooping cough and the ciliated epithelium lining the trachea and bronchi. The local effect produced by the organism is chiefly mechanical. It now remains to be demonstrated by experimental work whether or not the bacillus discovered by Bordet and Gengou will produce this same mechanical effect or lesion. If it does not then the true causal agent must be obtained in pure culture and tested in the same way.

Experimental work along these lines is now under way. It has proceeded far enough to enable us to state that sputum from an acute case of pertussis injected into the trachea of a puppy causes the same lesion to appear as is found in man, namely, masses of minute bacilli packed between the cilia of the lining epithelium.

SUMMARY AND CONCLUSIONS.

Whooping cough is due to a minute bacillus which occurs in large numbers between the cilia of the epithelial cells lining the trachea and bronchi and possibly also the nose. The location of the organism is apparently characteristic for the disease. Its action seems to be largely mechanical. It interferes by its presence with the normal movements of the cilia and possibly leads to their destruction.

The mechanical interference with the action of the cilia, and possibly their destruction, prevent the normal removal of secretion. The bacilli and the secretion produce a continuous irritation which results in coughing and usually also in the characteristic spasm known as whooping.

The bacillus found in the lesions is probably identical with the organism discovered and described by Bordet and Gengou, but this identity remains to be demonstrated by the experimental production of the characteristic lesion in monkeys and puppies.

Synopsis of Clinical Histories.

Case 1 (12.24). — Female, one year, two months old. Admitted March 6, 1912; died March 9, 1912.

Family history unimportant.

Previous history. — Was a full term, normally delivered baby. At age of twelve months had "pneumonia." From then until recently has not been well; has had a loose cough without expectoration. During these two months has been exposed to several cases of pertussis.

Present illness. — February 22, child began to whoop whenever she coughed; many paroxysms daily and six or seven at night, during which patient would "get black and couldn't catch breath." The paroxysms frequently ended with vomiting. Child has lost weight and has had "moderate fever during past two weeks." Lately her breathing has been rapid and she has been chilly and has had "sweats."

March 6. — Temperature 101° F. Pulse and breathing rapid. Coughs with decided whoop; became cyanotic and vomited during examination. Lungs disclose many moist crackling râles throughout.

Patient became steadily worse after admission. March 8, temperature 105° F., pulse 160, respiration 85; pulse weak, respiration shallow.

Post-mortem examination thirteen hours after death showed numerous fibrous adhesions in both pleural cavities, mucopurulent bronchiolitis, and areas of atelectasis.

Case 2 (12.25). — Female, two years, nine months old. Admitted March 18, 1912; died March 19, 1912.

Family history negative.

Past history. — At age of five months had diphtheria, otitis media, and abscess of neck. Two months before admission had measles and was ill for two weeks. Has been definitely exposed to pertussis several times during past two months.

Present illness. — During convalescence from measles patient began to cough and "whoop." Complained of sore mouth. One week ago began to have high fever with rapid breathing, loss of appetite, and fever at night. Has been gradually growing worse.

Physical examination. — Patient is cyanotic and has frequent paroxysms of coughing followed by vomiting.

Left ear presents a profuse discharge of mucoid material. Mouth and throat negative. Cervical lymph nodes slightly enlarged. In both lungs many coarse moist râles and broncho-vesicular breathing. In left lung an area of dulness in front from second to fifth rib and extending to left border of heart. Other organs negative.

March 19. — Since admission temperature has risen from 99° to 104° F.; pulse weaker and more rapid; respirations have increased from thirty-five to fifty per minute. Died same day.

Post-mortem examination two and one-half hours after death. The lungs showed numerous small foci of solidification not exceeding one

centimeter in diameter, varying from red to gray in color. The trachea showed slight exudation on its surface. Other organs negative.

Case 3 (97.300). — Male, two years, nine months old. Admitted Aug. 23, 1897; died Aug. 30, 1897.

Family and previous history negative.

Present illness. — August 14 began to cough, feel feverish, and complain of soreness in chest. August 21 began to whoop and vomited four or five times a night but not in day time.

Physical examination. — Well developed and nourished. No aural or nasal discharge. Lungs present numerous râles scattered throughout. Heart and other viscera negative.

August 30. — Since entry has coughed and vomited frequently; stools watery. Suddenly developed clonic convulsions; later under treatment became conscious and rational. Still later temperature became elevated, pulse weak and rapid, respirations shallow; child died three hours after convulsions.

Post-mortem examination practically negative. The vessels of the brain were congested and the pia was somewhat edematous. Lungs showed no foci of atelectasis or of bronchopneumonia.

REFERENCES.

1. Bordet et Gengou. Annal. de l'Instit. Pasteur, 1906, xx and xxi.
2. Klimenko. Centralbl. f. Bakt., Abt. I., Originale, 1908, xlviii, 64–76.

DESCRIPTION OF PLATES.

(The drawings are by Miss Etta R. Piotti, the photomicrographs by F. B. M. The magnifications of the photomicrographs are exact, of the drawings approximate).

PLATE XII., FIG. 1. — Ciliated epithelium lining normal trachea of child. x 1,000.

FIG. 2. — Ciliated epithelium lining trachea of child dying in acute stage of whooping cough. Large numbers of minute bacilli present between the cilia. x 1,000.

FIG. 3. — Ciliated epithelium lining bronchus of child; mucus forming in cells and collecting on surface. x 1,000.

FIG. 4. — Ciliated epithelium lining bronchus of child dying in acute stage of whooping cough. Masses of minute bacilli present between the cilia. x 1,000.

FIG. 5. — Minute bacilli present in masses between cilia of two cells lining trachea. x 1,500.

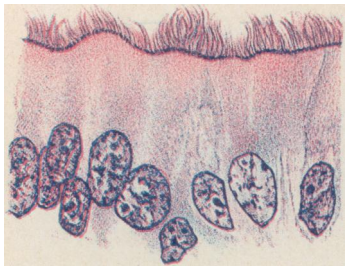
FIG. 6. — Desquamating epithelial cell in trachea with numerous bacilli between cilia. x 1,500.

FIG. 7. — Ciliated epithelium from trachea of child dying at a late stage of whooping cough. Bacilli still present in small numbers between cilia. x 1,500.

PLATE XIII., FIG. 1. — Ciliated epithelium lining trachea of child dying in acute stage of whooping cough. Masses of minute bacilli present between cilia. x 1,000.

FIG. 2. — Ciliated epithelium lining trachea from same case. x 1,500.

FIG. 3. — Ciliated epithelium lining trachea from child dying at a late stage of whooping cough. Bacilli still present in small numbers between the cilia. x 1,500.



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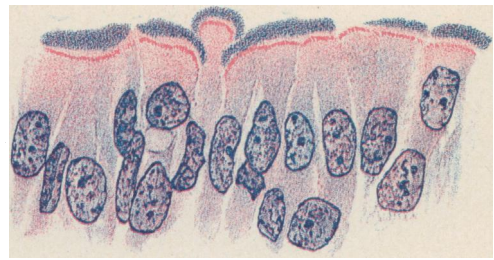

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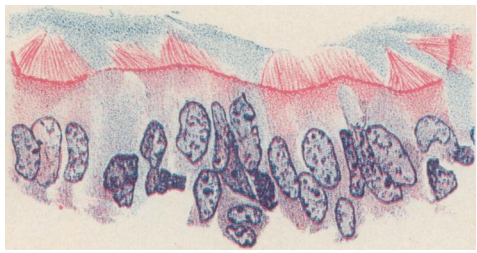

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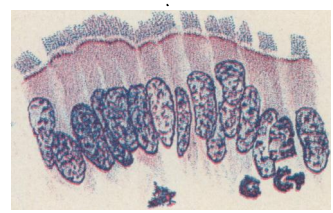

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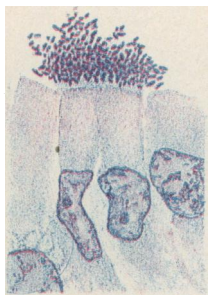

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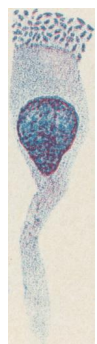

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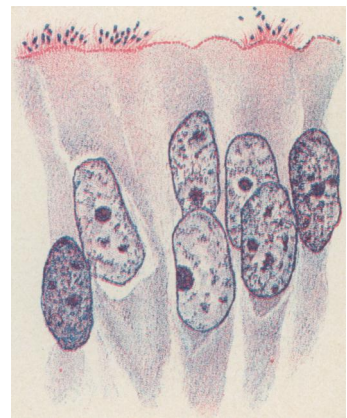

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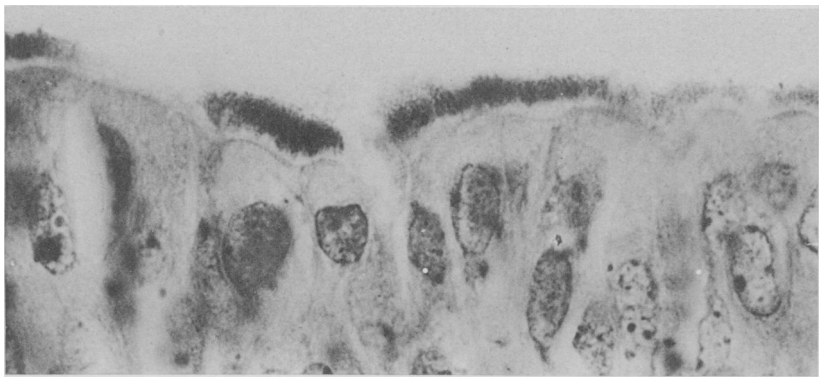

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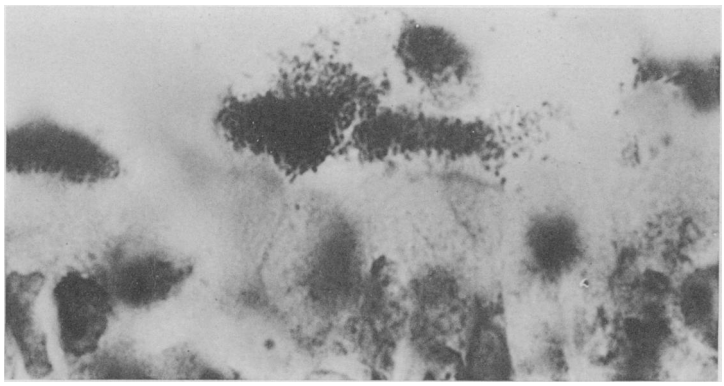

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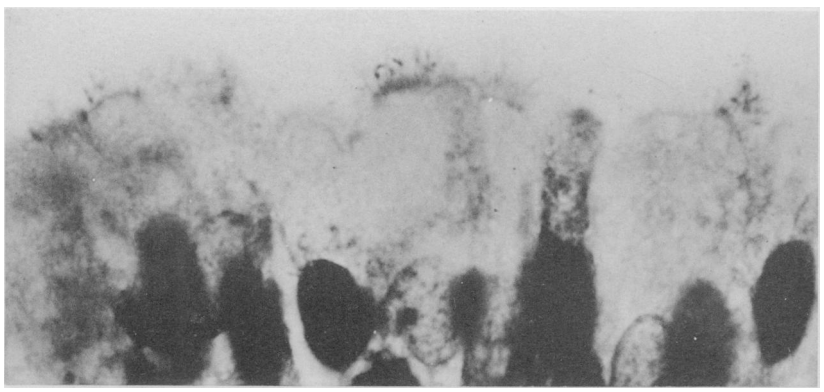

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