

With the Author's Compliments

Knyazev

*Bacteriological Investigations of Diphtheria
in the United States.*

*A Report in Behalf of the American Committee on
Diphtheria to the Eighth International Congress
of Hygiene and Demography, held in Buda-
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BY

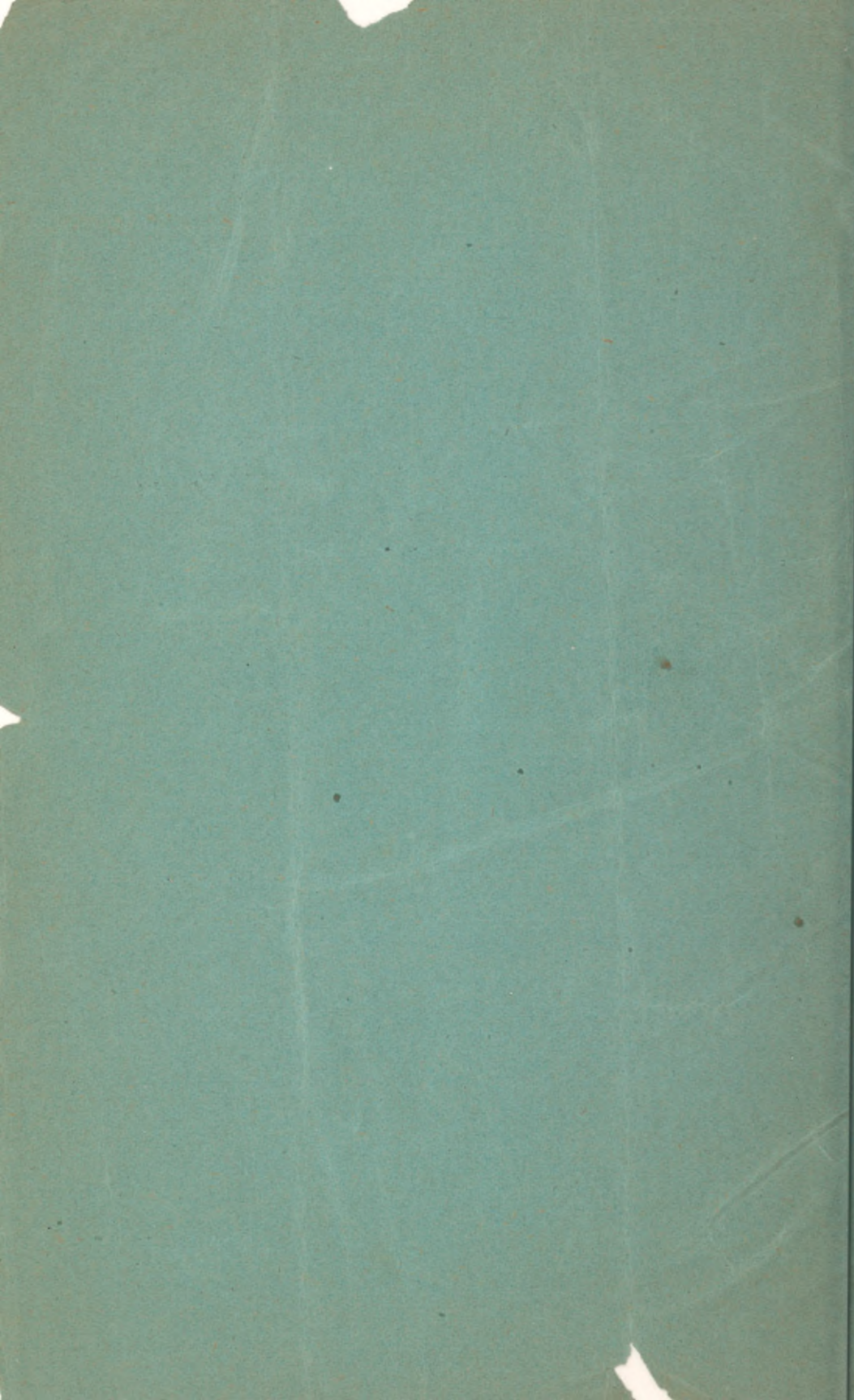
WILLIAM H. WELCH, M.D.,

PROFESSOR OF PATHOLOGY IN THE JOHNS HOPKINS UNIVERSITY, BALTIMORE.

FROM

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES,

OCTOBER, 1894.



BACTERIOLOGICAL INVESTIGATIONS OF DIPHTHERIA IN THE UNITED STATES.

A REPORT IN BEHALF OF THE AMERICAN COMMITTEE ON DIPHTHERIA¹ TO THE EIGHTH INTERNATIONAL CONGRESS OF HYGIENE AND DEMOGRAPHY, HELD IN BUDAPEST, SEPTEMBER 1 TO 9, 1894.

BY WILLIAM H. WELCH, M.D.,

PROFESSOR OF PATHOLOGY IN THE JOHNS HOPKINS UNIVERSITY, BALTIMORE.

It is intended in this report to present the more important results of the bacteriological study of diphtheria by American investigators, so far as these results are believed to be of interest for the purposes of this Congress.

The most extensive bacteriological researches on diphtheria in this country have been made by Prudden and Park in the Pathological and Bacteriological Laboratories of the College of Physicians and Surgeons, Columbia College, New York (Director, Dr. T. M. Prudden), and by Park (partly in co-operation with Beebe) under the Division of Pathology, Bacteriology, and Disinfection, Health Department of New York (chief of this Division, Dr. Hermann M. Biggs); by Welch, Abbott, Booker, and Flexner in the Pathological Laboratory of the Johns Hopkins University and Hospital (Director, Dr. W. H. Welch); by Koplik, working in the Carnegie Laboratory, Bellevue Hospital Medical College (under the direction of Dr. E. K. Dunham); by Abbott, Ghriskey and Ravenel in the Laboratory of Hygiene, University of Pennsylvania (under the direction of Drs. J. S. Billings and A. C. Abbott); by Councilman, Williams, Morse, Townsend, Wright and Emerson in Boston, chiefly in the Boston City Hospital, and in the Pathological Laboratory of the Harvard Medical School (Director, Dr. W. T. Councilman). The references to articles are given at the end of this paper.

The writer is indebted for original abstracts of their work (some of it hitherto unpublished) and their preparation for this report, to Drs. Prudden, Park, Koplik, Abbott, Ravenel, Booker, Morse, Wright, and Emerson; and he desires to express to these gentlemen his cordial thanks for their kind co-operation, and also to Dr. Councilman for procuring the abstracts

¹ This committee, of which Dr. John S. Billings is Chairman, was appointed by the Secretary General of the Eighth International Congress of Hygiene and Demography, together with similar committees in other countries, to report to the Congress upon various questions relating to diphtheria. To the writer was assigned the subject of this report.

of work done under his supervision. It was intended at first to publish *seriatim* these abstracts, but it is believed that a systematic presentation of the combined results under suitable headings will be more useful. The purposes and limits of this report permit the statement of only some of the results of American workers, and these often in much abbreviated form. The writer, whose part is only that of a referee, will make free use, often without further acknowledgment, of the words of the authors. The larger part of the investigations of Park reported in this paper are unpublished. This report embraces the results up to May, 1894.

In accordance with the programme of the Congress, especial attention will be given in this report to the results thus far obtained in the United States as to the following points:

The application and value of bacteriological methods in the diagnosis of diphtheria; the proportion of cases of pseudo-membranous inflammations of the throat and air-passages due to the Loeffler bacillus; the various localizations of the diphtheria bacillus; atypical forms of diphtheria, and false diphtheria; the persistence of the Loeffler bacillus in the throat after recovery from diphtheria; the occurrence of this bacillus outside of persons affected with diphtheria; the characters of pseudo-diphtheria bacilli.

HISTORICAL.—The first bacteriological study of pseudo-membranous inflammations of the throat by modern methods in this country was by Prudden in 1889. He studied by microscopical examination and cultures twenty-four cases diagnosticated as diphtheria in young children, most of them in New York hospitals in which the affection had assumed the character of an epidemic. In a few of these cases the pseudo-membranous inflammation occurred by itself, but in most of them it was associated with scarlatina, measles, or suppuration. In all but two of these cases he found a streptococcus, usually in large numbers in the local lesions and in small numbers in a few cases in the viscera. Loeffler's bacillus was not found in any of this group of cases.

Prudden has withdrawn the name streptococcus diphtheriæ, originally applied by him to the streptococcus found in these cases, which did not appear to differ from the streptococcus pyogenes. It is clear that the group of cases first studied by Prudden were not cases of genuine diphtheria, but were for the most part cases of secondary pseudo-membranous inflammations, which are now known to be oftener due to a streptococcus than to the Loeffler bacillus.

In February and March, 1891, Welch and Abbott published the results of the bacteriological examination of eight cases of primary diphtheria, in all of which the Loeffler bacillus was found.

In April, 1891, Prudden published the results in twelve cases of diphtheria unassociated with complicating lesions, and found the bacillus of Loeffler in all but one.

Since these first publications the number of cases of suspected or established diphtheria which have been examined bacteriologically in the United States, so as to be available for statistical analysis, has been between 6000 and 7000 (May, 1894).

Several hundred of these cases were examined in hospitals, dispensaries, and private practice, but by far the larger number were examined under the Health Department of the City of New York. Under the intelligent and efficient direction of Dr. Biggs the Health Department has entered upon an undertaking which, upon such a scale, is believed to be hitherto unparalleled, to wit: the systematic examination of all cases of suspected diphtheria (unless objection is made by the attending physician or except certain cases in which it is not deemed advisable to disturb the patient) occurring in New York—the study of the cultures thus obtained being made by Dr. William H. Park and Mr. Alfred Beebe, who are thoroughly trained and careful bacteriologists. Some of the results of this undertaking will be considered in this paper.

All the bacteriological aspects of diphtheria and other pseudo-membranous inflammations of the throat, with the exception of systematic study of immunization and serum-therapy, have been investigated by the various American workers already mentioned. Attention, however, will not be given in this paper to the purely morphological and cultural characters of the diphtheria bacillus, except as they relate to the question of differentiation of the pseudo-diphtheria bacillus.

TECHNIQUE.—In general the methods of examination have been those usually employed, and only a few points need to be especially mentioned.

To obtain the material for cover-slips and culture from the suspected throat, Park uses sterile cotton swabs made by wrapping firmly a small pledget of absorbent cotton around the roughened end of a thin, stiff steel rod six inches in length. These swabs placed in an equal number of glass tubes, plugged with cotton, are sterilized for one hour by dry heat at 150° C. A similar method is employed by Councilman and others in Boston. Koplik prefers, both to the cotton swab and to the ordinary platinum wire, especially for removing tonsillar plugs, a small sterilized thin scoop in the form of a long bent probe.

All are agreed as to the superiority of Loeffler's blood-serum mixture for making original cultures from the throat. The blood-serum mixture is now generally prepared by direct sterilization and solidification in the steam or hot-air sterilizer at a temperature a little below 100° C., instead of the old method of fractional sterilization at a lower temperature. The loss of transparency in the medium is compensated by the greater facility in preparation, and no difficulty is found in seeing the colonies after twelve to eighteen hours. Egg-albumen, as recommended by

Johnston, and urine agar were found by Park less satisfactory than blood-serum.

While recognizing that the bacillus of diphtheria grows well on agar when planted from cultures on blood-serum or other media, and that the agar colonies are the most characteristic and best adapted for microscopical study, Park calls attention to the uncertainty of glycerin-agar as a medium for making original cultures from the exudate. This uncertainty is due not only to unavoidable variations in the composition of the beef-broth, and to the less luxuriant character of the growth of the bacillus diphtheriæ as compared with its coincident growth with other bacteria upon blood-serum, but also to the observation that when the bacilli diphtheriæ are few in number or have been affected by previous application of antiseptics, they may fail to grow upon agar when blood-serum inoculated at the same time and with the same exudate presents growth of the bacilli. Of course, the use of antiseptics shortly before making the inoculation of the tube is likely to render the cultures useless.

When it is desired to determine accurately the kinds of bacteria associated in the exudate with the diphtheria bacillus, especially the presence of streptococci, it is desirable not to rely upon blood-serum alone, but to make also agar plates from the exudate.

In testing the virulence of diphtheria cultures emphasis is laid, in all of the later work, upon observing precautions which have been noted especially by Behring and by Escherich. Thus Koplik selects young guinea-pigs weighing from 350 to 450 grammes, and injects 0.1 to 0.5 cc. of a bouillon culture forty-eight hours old in the thermostat. The quantity injected should be taken from the full culture after shaking and not after pouring off the supernatant fluid from the deposit. Park also emphasizes the importance of selecting, if possible, young guinea-pigs and injecting $\frac{1}{4}$ to $\frac{1}{2}$ per cent., in special cases even 1 per cent., of the body-weight of a forty-eight hour bouillon culture grown at 37° C.

For ordinary diagnostic purposes cover-slip preparations and cultures are considered sufficient without awaiting the result of the animal experiment. In all of the cases both cover-slip preparations and cultures were made, and in many also inoculation of guinea-pigs.

METHODS ADOPTED BY THE HEALTH DEPARTMENT IN NEW YORK.—Under the Division of Pathology, Bacteriology, and Disinfection, of which the Director of the Bacteriological Laboratory is Dr. Hermann M. Biggs, and the Inspector of Diphtheria Dr. William H. Park, the Health Department of New York has organized a system which renders available to physicians throughout the city the bacteriological diagnosis of diphtheria, and which utilizes in the interests of preventive medicine the important discoveries relating to the causation

and mode of spread of diphtheria. These efforts have met, for the most part, with hearty co-operation on the part of physicians.

For carrying out this and similar work, a bacteriological laboratory has been equipped and competent bacteriologists and a force of physicians as inspectors are employed. Cultures are made, not only when specifically requested by physicians, but also when no objection is raised by the attending physicians, diphtheria being, of course, a notifiable disease. Especial attention is given to examinations in boarding-houses, hotels, and tenement-houses.

In general, cultures are not made for diagnosis from secondary cases in families where the first case was proven bacteriologically to be diphtheria, or in cases of croup in which tracheotomy or intubation has been performed, the knowledge to be gained by cultures in such cases being too slight to compensate for the disturbance of the patient. All such cases, and, in fact, all suspected cases in which cultures are not obtained, are regarded as diphtheria. Later cultures are, however, made to determine when the bacilli have disappeared and the premises are ready for disinfection.

Indeed, especial importance is attached to these later cultures, for in view of an extensive research to determine the length of time during which diphtheria bacilli may persist in the throat, the Health Department has adopted the rule, "That no person who has suffered from diphtheria shall be considered free from contagion until it has been shown by bacteriological examination, made after the disappearance of the membrane from the throat, that the throat secretions no longer contain the diphtheria bacilli, and that until such examinations have shown such absence all cases in boarding-houses, hotels, and tenement-houses must remain isolated and under observation. Disinfection of the premises, therefore, will not be performed by the department until examination has shown the absence of the organisms." Cultures are made also from the apparently healthy throats in an infected household for reasons which will appear later in this report.

The culture-tubes may be inoculated by the attending physician, if he so desires; otherwise the cultures are made by the inspector of the district in which the case occurs. The outfits for making the cultures, consisting of a box containing a tube of blood-serum and a sterilized swab in a test-tube, are distributed to about forty stations at convenient points throughout the city, these being mostly druggist shops. A list of these stations is published, at which physicians can obtain the outfit free of cost.

Printed directions for making the cultures in suspected cases of diphtheria are supplied with the outfit, and are as follows:

"The patient should be placed in a good light, and, if a child, properly held. In cases where it is possible to get a good view of the throat,

depress the tongue and rub the cotton swab gently, but freely, against any visible exudate.

"In other cases, including those in which the exudate is confined to the larynx, avoiding the tongue, pass the swab far back, and rub it freely against the mucous membrane of the pharynx and tonsils. Without laying the swab down, withdraw the cotton plug from the culture-tube, insert the swab, and rub that portion of it which has touched the exudate gently but thoroughly all over the surface of the blood-serum. Do not push the swab into the blood-serum, nor break the surface in any way. Then replace the swab in its own tube, plug both tubes, put them in the box, and return the culture outfit at once to the station from which it was obtained.

"A report will be forwarded the following morning by mail, or can be obtained by telephone, after 12 noon."

There follows a list of the stations from which the culture-outfits can be obtained free of cost.

The inoculated tubes and swabs are sent from the stations to collecting depots, whence they are taken by the collectors on the same day to the laboratory. There is filled out and returned with the cultures a printed form giving the name and address of the attending physician and of the maker of the culture, the date, the name, age, and address of the patient, the clinical diagnosis, various details relating to the supposed causation, the duration and character of the disease, the use of antiseptic applications, and a statement as to whether the inoculation was satisfactory. Another printed form is to be filled out for later cultures.

From time to time explanatory circulars as to the character and results of the work and the rules adopted by the department are issued to physicians.

There are printed forms to be filled out in reporting to physicians the results of the cultures; one form is for cases in which diphtheria bacilli are found; another is for cases in which the bacilli once present have disappeared, and on this is the statement that the case is ready for disinfection, if other circumstances allow; a third form is for cases in which the cultures do not show the presence of diphtheria bacilli; and a fourth in the case of cultures which do not permit an exact bacteriological diagnosis with a statement of reasons for the failure, and, if need be, another culture is requested.

Specimens of these various printed forms accompany this paper for the inspection of those attending the Congress.

The results thus far obtained by this system have been satisfactory. From May 4, 1893, to May 4, 1894, 5611 cases of suspected diphtheria were subjected to bacteriological examination, some of the results of which will be stated later in this report.

As to the reliance to be placed upon a culture in making a diagnosis,

Park states, as the result of the very large experience accumulated by the Health Department, "The examination by a competent bacteriologist of the bacterial growth in a blood-serum tube which has been properly inoculated and kept for fourteen hours at the body temperature can be thoroughly relied upon in cases where there is visible membrane in the throat, if the culture is made during the period in which the membrane is forming, and no antiseptic, especially no mercurial solution, has lately been applied. In cases in which the disease is confined to the larynx or bronchi, surprisingly accurate results can be obtained from culture, but in a certain proportion of cases no diphtheria bacilli will be found in the first culture, and yet will be abundantly present in later cultures. We believe, therefore, that absolute reliance for a diagnosis cannot be placed upon a single culture from the pharynx in purely laryngeal cases. The apparent mistakes, however, have been few. Cultures cannot be certainly relied upon after the membrane begins to disappear."

The great majority of physicians desire cultures to be made and appreciate the value of an accurate diagnosis. Cases which are proved not to be diphtheria are not required to be isolated and are not kept under supervision by the Department; until such proof, however, suspicious cases are treated as diphtheria.

The duration of the period of isolation and the time for disinfection are determined by the bacteriological examination in accordance with the rule already quoted. The increased value of statistics as to the distribution, prevalence, mode of spread, clinical characters, mortality, and treatment of diphtheria when the diagnosis is based upon a bacteriological examination, requires no especial emphasis. Some of the scientific results which have been obtained by Dr. Park and Mr. Beebe from this immense material will be mentioned later in this article.

PROPORTION OF CASES OF SUSPECTED DIPHTHERIA PROVED BY BACTERIOLOGICAL EXAMINATION TO BE TRUE DIPHTHERIA.—There are several points to be considered in estimating the value of statistics upon this point. The character of the cases selected for examination, whether wholly characteristic or less characteristic of diphtheria, will be of decisive influence. The degree of suspicion in a given case may be very slight, or one physician may consider the case highly suspicious or certain, and another may regard it as very doubtful or certainly not diphtheria.

It is particularly in the doubtful cases that a bacteriological examination is desired and is of the most importance. Diphtheria may occur without any false membrane and as an angina or tonsillitis of very mild character.

In statistics based upon the statements of a large number of physicians as to the character of a local exudate it doubtless may happen that simple pultaceous and purulent exudates may be mistaken for

genuine fibrinous exudates. The inclusion of cases of pseudo-membranous angina, occurring in scarlet fever or other diseases, or even during the prevalence of scarlet fever, will influence the statistical result. Special local conditions, such as the selection of cases exclusively from children's hospitals, and probably the time of year, may likewise have an influence upon the result. The care with which the cultures and cover-slip preparations are made and examined, the period of the disease at which they are made, the previous local application of antiseptics, are factors which will influence the result.

These considerations (and still others might be mentioned) may render the statistics of different observers not strictly comparable, and they indicate that some statistics are likely to be more accurate and valuable than others.

We owe to Park and to Morse the most extensive statistics as to the subject now under consideration. In his first published series Park examined 140 pseudo-membranous cases uncomplicated with scarlet fever, in which the clinical diagnosis of probable diphtheria had been made. He found the Loeffler bacillus in 54 cases (39 per cent.). Of the 86 remaining cases the membrane was confined to the tonsils in 58, and these latter were all mild.

In his second published series, 104 uncomplicated cases were examined and the Loeffler bacillus was found in 73 (70 per cent.). Dr. Park has kindly furnished the writer his later, as yet unpublished, statistics (partly in co-operation with Beebe), which will be included in a report to the Board of Health of New York. In this third series, 5611 cases or suspected diphtheria occurring in New York during the year ending May 4, 1894, were examined bacteriologically. A few of these cases complicated scarlet fever, but the precise number of such cases is not stated. The Loeffler bacillus was found in 3255 cases (58 per cent.), and was absent in 1540 cases (27 per cent.). In 816 cases, although no diphtheria bacilli were found in the cultures, yet either because the cultures were made after the fourth day of the disease, or because the exudate was imperfectly obtained from the throat, or because the culture media had become contaminated or were too dry, the cases were considered to be of a doubtful nature as far as the bacteriological examination was concerned. If the doubtful cases be thrown out, which, however, it is hardly fair to do, as most of them are considered by Park not to have been diphtheria, we have, in 4795 cases of suspected diphtheria, about 68 per cent. of cases of true diphtheria, and 32 per cent. which were not diphtheria.

Morse found, in 301 cases without scarlet fever admitted to the diphtheria ward of the Boston City Hospital, the Loeffler bacillus in 217 (72 per cent.).

If we add all of the cases of suspected diphtheria in Park's and

Morse's statistics we have 6156 cases, of which 3599, or 58.5 per cent., were proved bacteriologically to be true diphtheria. If we reject from Park's third series the cases in which the bacteriological examination was unsatisfactory we have 5340 cases, of which 67.5 per cent. were cases of true diphtheria.

Park's first series was remarkable on account of the small percentage of cases of true diphtheria. The examinations were made in February and March, and scarlet fever was very prevalent, diphtheria less so. His experience at this time he considers to have been exceptional, and it has not been repeated. His own conclusion is, from his later observations, that about 60 per cent. of the cases of suspected diphtheria in New York are true, and about 40 per cent. are false, diphtheria.

We are, of course, not to infer that only 60 per cent. of the cases which are considered by physicians to be undoubted diphtheria are really diphtheria, but that this is about the percentage of cases of genuine diphtheria in the pseudo-membranous inflammations of the throat in which there is more or less suspicion of diphtheria.

Upon each blank sent with a culture-tube by the Health Department of New York, a space is left for the voluntary recording of the clinical diagnosis by the physician. In 1210 cases of true diphtheria the physician's diagnosis was recorded. In 1011 the case was considered on clinical grounds to be diphtheria, in 102 to be doubtful, and in 87 to be probably false diphtheria. In 675 cases in which the diphtheria bacilli were absent a diagnosis of diphtheria was made in 50, the rest being all considered to be in doubt.

In this connection Park says: "The cases which present the characteristic appearances of well-developed diphtheria regularly contain in the pseudo-membranes abundant diphtheria bacilli. It is the slightly developed cases in which a culture is most needed. Here without cultures we need to go more by the history of exposure than the appearance of the case. In a family where an undoubted case of diphtheria existed, any form of sore throat, with or without exudate, in a child or adult, would be probably a case of diphtheria, while a similar-appearing tonsillitis or pharyngitis in a person who had not been exposed to diphtheria would be, in all probability, a case of ordinary non-diphtheritic throat inflammation." In only about one-half of the cases of diphtheria examined by the Health Department of New York did careful inquiry reveal any connection with other diphtheria cases.

The statistics which have been cited are based upon the examination of pseudo-membranous inflammations of the throat and air-passages mostly uncomplicated with scarlet fever.

Of particular significance is the outcome of Morse's study: that in no less than 28 per cent. of the cases admitted to the diphtheria ward of the Boston City Hospital, diphtheria bacilli were not found.

MEMBRANOUS CROUP.—Welch and Abbott, Booker, Williams, and others have reported cases of diphtheria in which the pseudo-membrane was confined to the larynx and lower air-passages. In Park's statistics there are 286 cases (283 children and 3 adults) in which the membrane was entirely or chiefly confined to the larynx or bronchi. In the cultures from 229 of these the Loeffler bacillus was found, and 167 of these 229 cases showed no pseudo-membrane or exudate above the larynx, while in the remaining 62, although the larynx was mainly involved, there was also some membrane or exudate present on the tonsils or pharynx. In the remaining 57 no diphtheria bacilli were found, but of these, the cultures in 17 were unsatisfactory, leaving the bacteriological diagnosis doubtful. In the 40 cases in which the diphtheria bacilli were absent the disease was confined to the larynx or bronchi in 27, while more or less exudate or membrane was present on the tonsils or pharynx in 13. Of the cases of membranous croup in New York, therefore, at least 80 per cent. are diphtheria and only 14 per cent. were undoubtedly not diphtheritic. Cases of membranous croup were observed to be the origin of cases of characteristic pharyngeal diphtheria.

The comparatively small number of laryngeal cases examined is accounted for by the custom of the department inspectors not to make cultures in cases which have been intubated or which seem so sick that the family might think injury had been done by inserting the swab.

In a personal communication Dr. Park writes that he has no doubt as to the occurrence of non-diphtheritic pseudo-membranous laryngitis. He speaks of two cases in which the microscopical examinations and cultures made both during life and after death showed no diphtheria bacilli, but streptococci were present. Booker has reported such a case complicating measles.

FIBRINOUS RHINITIS; NASAL DIPHTHERIA.—Park reports 10 cases of fibrinous rhinitis in all of which the Loeffler bacillus was found. All were typical and of the usual benign character. In 9 the membrane was confined to the nose, and in one there was also slight fibrinous exudate on the tonsils. Only the 6 cases in his first series are reported in detail. In 4 the Loeffler bacillus was associated with streptococci and in 2 with staphylococci. The virulence of the diphtheria bacillus was tested in 5 cases. The bacillus from one case killed a guinea-pig in four days; those from two cases in five days, and those from two other cases rendered the guinea-pig sick, but the animals eventually recovered. In addition to this weakening of virulence Park found that the bacilli from the first six cases grew more feebly than usual both on blood-serum and agar, and died out in cultures sooner than usual.

Abbott has published 3 cases of fibrinous rhinitis, and Ravenel, working under Abbott's direction, has kindly sent me an account of 2 additional cases which he will publish. All of these 5 cases were of benign

character, the membrane being confined to the nasal cavity. Two were in sisters in the same family. In all the Loeffler bacillus was present in the membrane; in 3 it was of the customary virulence, and in 2 it produced only local reaction, in large doses failing to kill even half-grown guinea-pigs.

Townsend observed in 14 cases of diphtheria, mostly of mild character, occurring in the Children's Hospital in Boston, 7 cases in which the nose was affected. Of the latter, in 5 cases the disease was primarily nasal, the membrane being confined to the nose in 4. These 4 cases of primary and exclusively nasal diphtheria were mild. In all the Loeffler bacillus of customary virulence was found. He emphasizes the case with which these primary nasal cases may be overlooked if the membrane remains confined to the nose, the importance of a bacteriological examination in all suspicious cases of nasal discharge, the mild character of many of the cases, their resemblance by superficial examination in some cases to an ordinary coryza, and the danger of such cases as sources of infection.

Park mentions an instance in which a child with only a slight nasal discharge, in which Loeffler bacilli were demonstrated, gave rise to diphtheria in four children, of whom two died. The first child came from a family in which there had been a case of diphtheria three weeks before.

CLINICALLY ATYPICAL DIPHTHERIA.—The most important bacteriological study of this subject has been made by Koplik, who has kindly furnished the following abstract of his work:

The writer has for the past three years directed his attention chiefly to the study of those forms of diphtheria which clinically do not present any of the classical local symptoms of the disease. The direct outcome of these studies has been to demonstrate how multiform diphtheria may be, from a clinical standpoint, in its various local manifestations. The first series of studies was published in the *New York Medical Journal*, August 27, 1892, and *Archives of Pædiatrics*, September, 1892. In these papers the writer gave the results of studies of the following forms of diphtheria:

A. Cases in which there is from the onset and through the whole course of the disease no local manifestation of membrane, either *diffuse* or *punctate*. These cases may be so exceedingly mild in their course as to simulate a simple catarrhal angina, or they may be accompanied not only by anginal symptoms, but laryngeal symptoms, such as croupy cough and croupy breathing. In the latter case, early in the disease, we find upon the most careful inspection of the fauces no signs of membrane; later, this picture may persist, or there may appear punctate areas of membrane upon the tonsils or pillars of the fauces. The point of greatest moment, however, is that at first and for days the closest inspection of the fauces and epiglottis reveals no signs of membrane. The croupy cough and breathing reveals involvement of the larynx. Where only the cough is manifest it is to be presumed that in

the larynx the condition is much like that found in the throat, an intense inflammation without membrane.

It is, of course, impossible to establish the exact anatomical conditions. In these cases I have fixed the diagnosis of diphtheria by scrapings from the tonsil and fauces. The most dangerous of these cases in spreading infection are those which present symptoms of a mild catarrhal angina. The writer has published a series of cases occurring in the same family of children who presented these mild anginal symptoms. They communicated their anginal diphtheria to one another. Some of the cases developed membrane (punctate, in other cases diffuse of fauces and larynx), resulting in fatal laryngeal stenosis. On the other hand, the writer has published a series of cases of children who presented all symptoms of acute catarrhal angina, with signs of lacunar amygdalitis. In these cases the croupy cough and breathing were not present. These were not diphtheritic. The only test is the bacteriological one.

B. A class of cases in which the tonsils are covered by a pultaceous mass of exudate, and no consistent membrane. These cases may or may not be true diphtheria.

C. A large class of cases presenting punctate form of membrane; some of these spots of membrane may be isolated and minute on the tonsil; in some forms the specks of membrane are depressed in the surface of the tonsil. In other forms minute or larger ulcerations exist. These cases may be diphtheritic, and in the vast majority of cases are true diphtheria. In other cases we fail to find the Loeffler bacillus.

D. The most important class of clinically atypical diphtherias are those cases which begin or even run their entire course with the clinical local picture of a typical lacunar or follicular amygdalitis. In my last paper, entitled "Acute Lacunar Diphtheria of the Tonsils" (*New York Medical Journal*, March 10, 1894) these cases are divided into groups. In the first group of cases the course of the disease is that of an exceedingly mild lacunar or follicular amygdalitis. The fauces are injected, the tonsils are enlarged, there is an indication here and there of a lacuna, by a yellow spot; the lymph-glands at the angle of the jaw may or may not be enlarged; the constitutional symptoms are almost *nil*. Extraction of the contents of the lacunæ or follicles shows the presence of the bacillus diphtheriæ.

In the second group of cases the tonsils are more inflamed, the lacunar plugs protrude from the tonsils in the form of soft fibrinous masses; the patients seem quite ill, as if suffering from a severe amygdalitis. In these cases also the lacunar plugs are found to contain the Klebs-Loeffler bacillus in almost pure culture. Here also glandular nodes are found at the angle of the jaw. The course of these cases clinically is interesting; some never develop membrane as a mass on the tonsils; others after the third day develop distinct thick confluent membrane on the tonsils. Others remain lacunar in the local tonsillar picture, but develop laryngeal diphtheria, with croupy cough and breathing. In this class the lymph nodes at the angle of the jaw may be much enlarged in packets, or not much above what is found in ordinary anginas. These cases may give rise to other cases in the same family in which the course of the disease is that of a simple lacunar amygdalitis, but which upon examination prove to be true diphtheria.

The third group of cases are those in which the disease begins with

the picture of severe lacunar amygdalitis, but the prostration of the patient is exceedingly great; the temperature may be low. There is great glandular swelling at the angle of the jaw. After a few days the prostration is much greater; there appears nasal discharge, and small shreds of membrane are discharged from between the much swollen tonsils. The tonsils themselves are now covered with one continuous membrane, but here and there shreds are seen on the surface of the eroded tonsil. These cases are the septic lacunar diphtherias with nasal symptoms, and give a bad prognosis.

In a series of 39 cases of acute lacunar or follicular inflammation of the tonsils, 12 were proven to contain the Loeffler bacilli in the depths of the tonsillar lacunæ. Thus, fully one-third of the cases were diphtheria. It is not intended to draw any percentage conclusion from this, but it demonstrates how insidious an affection lacunar amygdalitis may be. (*New York Medical Journal*, March 10, 1894.)

Diphtheria sine membrana has been observed also by several other American investigators. Reference has already been made to Park's statement that any form of sore-throat in a person exposed to diphtheria is likely to be referable to the diphtheria bacillus. He says: "Under diphtheria should be included all inflammations of mucous membranes due to the diphtheria bacillus of Loeffler. A case with an acute hyperæmia of the mucous membrane in which the Loeffler bacilli are present is considered as truly a diphtheria as one with pseudo-membrane or exudate." Only the bacteriological examination can determine the true character of these cases. It is to be borne in mind, as pointed out by Councilman, that the absence of the pseudo-membrane in the places where it is ordinarily found is not proof that it is not present elsewhere, perhaps in some place not accessible to examination.

OTHER LOCALIZATIONS OF THE DIPHTHERIA BACILLUS AND ITS DISTRIBUTION AT AUTOPSIES.—Councilman has found the diphtheria bacillus in one case of otitis media following diphtheria and in two cases of otitis media, without affection of the throat, in measles. Townsend observed a case in which an old tracheotomy wound was attacked and the disease spread to the bronchi, proving rapidly fatal, with demonstration of the Loeffler bacillus. Park found diphtheria bacilli in two cases in wounds of the finger received by physicians in intubating children with diphtheria. In one case the bacilli persisted in the wound for six weeks. Wright (unpublished results communicated to the writer) has demonstrated the presence of this bacillus in excoriated or ulcerated surfaces of the skin in 7 cases, in paronychia in 1, in mastoid abscess in 1, in purulent conjunctivitis in 1—all in cases of diphtheria. At autopsy he cultivated the bacillus from the ecchymotic mucous membrane of the stomach in 2 cases, and from œdematous tissue behind the œsophagus in 1. Wright also reports that in 10 out of 14 autopsies in cases of diphtheria broncho-pneumonia was present, and that in 9 cases the Loeffler bacillus was found in the lung, and in the re-

maining case only the streptococcus. In 7 of the 9 pneumonias streptococci accompanied the Loeffler bacillus, as well as in two other lungs in which no pneumonia existed. In 3 or 4 pneumonias the diplococcus pneumoniae was also present. The staphylococcus pyogenes aureus was also met in 4 pneumonias, once with the Loeffler bacillus and three times in company with all of the three bacteria just mentioned. Flexner has found the Loeffler bacillus in two broncho-pneumonias complicating diphtheria, and by microscopical examination of sections demonstrated Loeffler bacilli, mostly within leucocytes, in the broncho-pneumonic exudate. In both cases the diplococcus pneumoniae was, however, the predominant organism.

Howard has reported a case of acute ulcerative endocarditis (without diphtheria) with infarctions in the spleen and kidneys, in which, both by cultures and microscopical examination, bacilli indistinguishable morphologically and in cultures from the diphtheria bacillus, but devoid of virulence, were found abundantly and in pure culture in the valvular vegetations, the spleen, and the kidneys.

As to the presence of the diphtheria bacillus in internal organs at autopsy Booker reports a case of diphtheritic laryngitis in which at autopsy Loeffler bacilli were found in the blood, spleen, and lungs. Wright has found this bacillus out of 14 cases dead of diphtheria in the lung in 13 cases (9 with broncho-pneumonia), in the liver in 3, in the spleen in 2, in the cervical or bronchial lymph-glands in 5, in the kidney in 1, in the blood in 1, and in the mesenteric lymph-glands in 2. In 7 of these cases there was streptococcus septicæmia and in 2 a similar poly-infection with the staphylococcus pyogenes aureus. Two of the autopsies showed no marked lesions of diphtheria in the throat or trachea, the nasal cavities not having been examined. Both yielded virulent Loeffler bacilli—in one from the cervical lymph-glands and in the other from the pharynx. In both the bacillus was found in the air-passages. The bacillus, with slight virulence, was found also in certain of the organs in 3 autopsies on cases apparently not dead of diphtheria.

In guinea-pigs dead of experimental diphtheria, Wright found the diphtheria bacillus in the liver in 19 out of 155 cases, in the spleen in 15 out of 152 cases, in the heart's blood in 7 out of 153 cases, and in the kidney in 4 out of 151 cases.

Both in these as well as in the human cases the bacilli were found in the organs in but very small numbers, as a rule.

In three guinea-pigs the bacillus has been recovered by Wright from the seat of inoculation thirty-one to thirty-eight days after the date of inoculation.

Abbott and Ghriskey have observed frequently after inoculation of diphtheria bacilli into the testicles, less frequently after subcutaneous inoculation, of guinea-pigs, small nodules in the omentum composed

mostly of polynuclear leucocytes and containing the bacilli in large number.

Welch and Flexner have described in detail the histological changes in experimental diphtheria, and have shown that these are characterized especially by widely distributed areas of cell death with nuclear fragmentation. They have demonstrated that the local fibrinous exudate may be caused by dead, as well as living, diphtheria bacilli, and that the other lesions are referable to toxic products of the bacillus.

BACTERIA ASSOCIATED WITH THE DIPHTHERIA BACILLUS.—All of the investigators have found, as a rule, other bacteria associated with the Loeffler bacillus in the local exudates of diphtheria, although this bacillus is the only one which is constantly present. The most common associated micro-organism is the streptococcus pyogenes. Other bacteria which have been found are the regular buccal bacteria, the micrococcus lanceolatus, the staphylococcus albus and aureus, the bacillus coli communis (Morse), unnamed cocci and unnamed bacilli. Among these bacilli may be specified a short oval, slightly pointed bacillus, growing in long chains, running parallel to each, forming grayish-white colonies on agar not unlike those of the Loeffler bacillus. This bacillus was frequently encountered by Welch and Abbott. Morse describes a short, motile, liquefying bacillus and a non-motile diplo-bacillus growing invisibly on potato and not growing on gelatin. The only associated bacteria which are believed to exert pathogenic action are the streptococci, the pyogenic staphylococci, the micrococcus lanceolatus, and a coccus observed by Koplik which he considers to be identical with that described by Roux and Yersin and by Martin. Differences, mostly of a minor character, have been noted both in morphology and cultural characters between the different streptococci, but they are not considered sufficient to establish definitely different species.

It is regarded as established by all the investigators that the course and symptoms of diphtheria may be definitely influenced by these associated pathogenic bacteria, particularly by the most common of all, the streptococcus pyogenes. Cases of general streptococcus septicæmia accompanying diphtheria have been observed, especially by Councilman and his co-workers. Broncho-pneumonias, suppurations of lymph-glands and the so-called septic forms of diphtheria are attributed to these associated bacteria, especially to the streptococcus. It does not appear, however, either from the statistics of Park or of Morse, that the mortality is materially higher in cases of diphtheria in which the streptococcus is associated with the Loeffler bacillus than when the Loeffler bacillus is present without streptococci. In fact, the tables of Morse show a higher mortality when the Loeffler bacillus is associated with pathogenic staphylococci than with streptococci. Morse, however, does not attach decisive weight to this inference, as only in 25 cases did he

attempt a thorough differential study of all associated bacteria. Such study will always show the presence of other bacteria. In these 25 cases he found the streptococcus in 19 cases (9 without other bacteria in culture, except the Loeffler bacillus, 6 with staphylococcus aureus or albus, or both), and staphylococcus aureus or albus in 10 cases (4 alone, except the Loeffler bacillus). The general mortality in these 25 cases was 56 per cent., the mortality in the cases with the Loeffler bacillus and streptococci alone, 33 per cent., with Loeffler bacillus and staphylococci alone, 66 per cent., and with Loeffler bacillus, streptococci, and staphylococci, 66 per cent. As Morse says: "Statistics compiled from so small a number of cases are of little value." A similar conclusion as to the greater harmfulness of staphylococci than of streptococci is reached by Morse, contrary to the generally accepted opinion, also from the analysis of his larger table of 400 cases (301 without scarlet fever); but he admits that the comparatively small number of cases in which the streptococcus was found associated with the Loeffler bacillus (191 cases) may have been due to failure to recognize the minute, slow-growing colonies of streptococci in the twenty-four-hour blood-serum tubes, and the arrangement of the cocci on cover-glass specimens alone is not decisive as to the diagnosis of staphylococci, which were found in 295 cases. A minute and careful differentiation of the bacterial species was attempted by Morse in only 25 cases. We cannot, therefore, consider it established that staphylococci are more harmful than streptococci, especially as this inference is opposed to that of other investigators, and as Morse doubtless often overlooked the presence of streptococci.

PSEUDO-MEMBRANOUS INFLAMMATIONS OF THE THROAT IN SCARLET FEVER, MEASLES, AND TYPHOID FEVER.—In an epidemic of scarlet fever in Baltimore at the time when the city was unusually free from diphtheria, one-half of the cases seen by Booker had pseudo-membranous affection of the throat. He has reported 11 cases of pseudo-membranous angina (2 fatal) complicating scarlet fever, and 1 case of similar angina without exanthem in a family three members of which had scarlatina. In all of these cases, as well as in 4 scarlatinal anginas without pseudo-membrane, Booker found streptococci as the predominant organisms, and in none was the Loeffler bacillus present. In one case croupous conjunctivitis due to streptococci was associated with the pseudo-membranous angina. The staphylococcus aureus was found in 11 cases without apparent influence on the severity of the case. No difference was observed between the early and the late pseudo-membranous anginas as regards the bacteria present. He attributes the absence of true diphtheria from so large a number of cases of scarlatina as due to the freedom of the city from diphtheria at the time. Booker describes with much detail the morphological and biological characters of the streptococci

found, and divides them into groups, but these details will not here be considered.

Park in his first series of 159 cases reports 19 cases of pseudo-membranous inflammation of the throat complicating scarlatina. In 17 streptococci predominated, and in only 2 were Loeffler bacilli present, these latter presenting diphtheritic laryngitis. Staphylococci were met in only a few cases.

The experience in Boston, as reported by Williams and by Morse, has been exceptional in the large proportion of cases of true diphtheria complicating scarlet fever. Of 97 cases of scarlet fever in the Boston City Hospital, of which 35 came from two homes for children, reported by Williams, membranous throats were present in 35. Of these 12 were due to the Loeffler bacillus, and in 23 the Loeffler bacillus was not found. In the 23 pseudo-diphtheria cases the membrane was limited to the tonsils in 5 only, and in 3 it extended to the larynx. Of the 62 cases of scarlet fever alone, 8 died (13 per cent.), of the cases of scarlet fever with diphtheria 6 died (50 per cent.), of the 23 cases of scarlet fever with pseudo-diphtheria 5 died (22 per cent.). In a previous series of 86 cases of scarlet fever, of which 19 were complicated with membranous throats, but no bacteriological examination was made, the mortality in the latter group was 47 per cent., while in the 67 cases without membranous throats only 4½ per cent. died.

In Morse's paper are probably included some of the cases reported by Williams, as the observations of both are from the Boston City Hospital. Morse reports 99 cases of pseudo-membranous inflammation of the throat complicating scarlet fever. Of these 26 per cent. died. The Loeffler bacillus was found in 23, with a mortality of 43 per cent., and was not found in 76, with a mortality of 21 per cent. In the pseudo-diphtheric cases streptococci were present in 61, staphylococci (in 12 alone and in 57 with streptococci) in 69, and other bacteria in 3 cases. Mention has already been made of the large number of staphylococcus cases in general in Morse's statistics.

It is the opinion of Morse, and of Councilman, under whose direction Morse worked, that the large proportion of cases of combined scarlatina and diphtheria was due to contagion in the hospital where the conditions were unfavorable for proper isolation. These unfavorable conditions will be remedied in the new hospital for infectious diseases now building. A few of the mixed cases, however, were admitted with double infection as shown by bacteriological examination at entrance. Most of the cases came from tenement-houses. In Williams' cases the fact that 35 came from two public institutions may explain in part the large number of associated infections.

In contrast with these results in Boston it is interesting to note the observations of Booker, already cited, at a time and place in which

diphtheria was notably absent. It is evident that the proportion of cases in which true diphtheria complicates scarlet fever depends largely upon local conditions, these relating to the prevalence of diphtheria and the opportunities for contagion.

Booker reports three cases of pseudo-membranous inflammation accompanying measles. In all, streptococci and the staphylococcus aureus were found, and in none the Loeffler bacillus. These cases occurred during the same period as the scarlatinal cases, when the city was exceptionally free from diphtheria. In two cases the membrane was limited to the larynx, there being no visible exudate. One of these was fatal, and at the autopsy the whole larynx was covered by a tough, very loosely adherent, false membrane. Both microscopical examination and cultures of the membrane after death, as well as those made from the pharynx during life, failed to show Loeffler bacilli. This case, therefore, is a particularly conclusive one of the occurrence of membranous laryngitis without diphtheria. The third case presented pseudo-membrane on the tonsils, pharynx and conjunctivæ. Streptococci predominated with some colonies of the staphylococcus aureus.

In Park's first series of cases there is one case of laryngeal diphtheria accompanying measles. Loeffler bacilli were present. The child recovered after intubation. In another case, in which there was membranous laryngitis without diphtheria bacilli in the pharynx, measles developed on the eighth day. Intubation had been performed and was followed by recovery.

Williams reports one case of measles with diphtheria. This case, however, may be the same one as appears in Morse's statistics, who reports four cases of measles with severe throat symptoms giving rise to the clinical diagnosis of diphtheria. One contained a few Loeffler bacilli and many staphylococci. Of these two died. Six cases had measles and scarlet fever together, but it does not appear that any of these had membranous throats. All recovered, and the Loeffler bacillus was not found in any. Streptococci were present in 5, staphylococci in 2, and the diplococcus lanceolatus in 2.

Of particular interest are four cases of typhoid fever complicated by diphtheria, reported by Morse. At least three of the cases developed diphtheria after admission to the hospital. One was a patient ill with typhoid fever in a private room. A nurse, several days after leaving the scarlet fever ward, had a sore-throat, and was put in the same room over night. On the discovery of the Loeffler bacillus in her throat the next day, the nurse was transferred to the diphtheria ward. Four days later the patient with typhoid fever developed sore-throat with membrane containing the Loeffler bacillus. The next day a typical scarlet-fever rash developed, which was followed by desquamation. She ultimately recovered. One of the four patients died. At the autopsy

were found lesions of typhoid fever with diphtheritic pharyngitis, tonsillitis and laryngitis. Loeffler bacilli were demonstrated both *intra vitam* and *post mortem*. In addition, typhoid bacilli and general streptococcus infection were found in cultures after death. Wagner has already called attention to the greater frequency of pseudo-membranous affections in typhoid fever when diphtheria is prevalent.

PSEUDO-DIPHTHERIA.—The name pseudo-diphtheria is used by Park, Williams, and others to designate pseudo-membranous inflammations of the throat and air-passages not caused by the bacillus of diphtheria. The name is, for several reasons, objectionable, but no convenient substitute has been suggested. The term streptococcus diphtheritis fits most of the cases, but not all. The pseudo-diphtheria bacillus is not concerned in the causation of pseudo-diphtheria, or, if so, only in a very small number of cases.

We have just seen that the great majority of cases of pseudo-membranous angina in scarlet fever are due to streptococci, although under special conditions the proportion of diphtheritic cases may be exceptionally large.

The statistics as to the proportion of cases of pseudo-membranous inflammations of the throat not due to the diphtheria bacillus, exclusive of scarlatinal cases, occurring in New York and Boston, have already been given under the headings "Proportion of Cases of Suspected Diphtheria Proved to be Diphtheria," and "Membranous Croup." From these it appears that from about 28 to 40 per cent. of the cases of non-scarlatinal pseudo-membranous anginas are pseudo-diphtheria, the percentage in some series being larger and in others smaller. The high percentage of such cases in Park's first series is altogether exceptional and probably due to special circumstances, among which Park mentions particularly the prevalence of scarlatina, the relative infrequency of true diphtheria, and the season of the year (February and March). Park writes that since then he has found the diphtheria bacillus in a series of cases in over 80 per cent.

Several foreign writers have been impressed with the large number of American cases of pseudo-membranous angina and laryngitis in which diphtheria bacilli were not found, and have expressed some doubt as to the accuracy of the results. We attribute the striking differences in the reported statistical results of different investigators mainly to the class of cases selected for examination. If only typical and characteristic cases of diphtheria, be selected, as has been done by some observers, the proportion of cases in which the diphtheria bacillus is missed will be small, and may be *nil*. If, however, the less characteristic cases of diphtheria, concerning which, in many instances, no one can be sure without bacteriological examination whether they are genuine diphtheria or not, be included, there may be a relatively large percentage of

cases of pseudo-diphtheria. Foreign statistics, based upon the examination of cases admitted to the diphtheria wards of hospitals, in which cases, therefore, the clinical diagnosis is diphtheria, such as the statistics of Baginsky, in Berlin, Martin, in Paris, and Jansen, in Switzerland, agree substantially with the New York and Boston statistics.

Koplik and Park describe with much detail the anatomical and clinical characters of the less characteristic diphtheritic and of the pseudo-diphtheritic cases. Koplik's observations as to the former have already been cited. In these less characteristic cases neither the location nor the character of the diphtheritic inflammations of the throat suffice to distinguish positively the true from the false diphtherias, and a positive diagnosis must rest upon the bacteriological examination.

In the great majority of cases which have been examined with sufficient care, a streptococcus, not differing apparently from the streptococcus pyogenes or erysipelatis, has been the predominant organism in pseudo-diphtheria and is believed to be the cause of this affection. In a small number of cases generally, but in Morse's examinations in a large number of cases, staphylococci appear to have been the causative micro-organism. In a still smaller group of cases the diplococcus lanceolatus has been assigned as the causative factor. Koplik has met the coccus of Roux and Yersin. He also reports four cases of tonsillitis without membrane in which the pseudo-diphtheria bacillus was found without the typical virulent diphtheria bacillus.

Park reports the mortality in 408 consecutive cases of pseudo-diphtheria bacteriologically examined in New York, and not complicating scarlet fever, to have been only 1.7 per cent. Of the seven fatal cases only two were over five years of age. The five deaths in young children were all in laryngeal cases. He considers that nearly all of the deaths in pseudo-diphtheria are due to complications, the most important being scarlet fever, membranous laryngitis, and broncho-pneumonia. At the same period the mortality from true diphtheria in New York was 27 per cent.

In striking contrast to this low mortality in pseudo-diphtheria is that found by Morse in the Boston City Hospital, where 25 per cent. of the pseudo-membranous cases without Loeffler bacilli and without scarlet fever died. The difference between Park's and Morse's results is probably to be explained by the fact that Park's cases were largely the usual mild ones in private practice, whereas Morse's cases were of sufficient severity to be sent to the hospital, many being laryngeal cases, and many dying within twenty-four hours after admission, the great majority being young children from crowded and insanitary tenement districts. The mortality in true diphtheria uncomplicated with scarlet fever was in Morse's cases 41 per cent. Park also has noted the greater mortality of pseudo-diphtheria in the hospital cases as compared with those in private practice.

As is well known, there is much difference of opinion among physicians as to the contagiousness of throat affections due to streptococci and other cocci. In order to determine this point, the Health Department of New York, as reported by Park, investigated 113 consecutive cases of pseudo-diphtheria occurring in 100 families, and at the same time 70 consecutive cases of diphtheria in 50 families. A history of contact with another case was found in 14 of the 113 cases of pseudo-diphtheria, and in 33 of the 70 diphtheria cases. In 9 of the 100 families with pseudo-diphtheria there was more than one case, and in 13 of the 50 families with diphtheria there was more than one case. It did not seem in an investigation of 500 cases of pseudo-diphtheria that secondary cases were any less liable to occur where the primary case was isolated than where it was not. It is considered that where two cases occurred in a family together, or within a short period of each other, they may have been due to some common exposure rather than to direct contagion. Park believes that in the majority of cases of pseudo-diphtheria the streptococci concerned are those already existing in the healthy throat, and that the presence of certain infectious diseases and exposure to cold, dampness, and insanitary surroundings, are among the exciting causes. While not denying the possibility of contagion, he considers that the degree of communicability is only moderate and of minor importance. Even admitting the possibility of contagion, he argues that the very slight mortality in uncomplicated pseudo-diphtheria justifies the rule of the Health Department in not keeping this class of cases under supervision after they have been proved bacteriologically not to be true diphtheria. The question of isolation is thus left to the discretion of the attending physician.

That a comparatively small number of cases of membranous croup are due to streptococci has already been stated. Woods has reported two cases of croupous conjunctivitis following measles, in which streptococci, but no Loeffler bacilli, were found.

PERSISTENCE OF DIPHTHERIA BACILLI IN THE THROAT DURING AND AFTER CONVALESCENCE FROM DIPHTHERIA.—During the ten months preceding May, 1894, Park with his co-workers in the Health Department of New York has examined 752 cases of diphtheria with reference to the length of time the diphtheria bacilli remain in the throat. Cultures were made at the beginning of the disease, and again at short intervals after disappearance of the exudate, until the throat was found free of diphtheria bacilli. The custom was to make the second culture three days after the complete disappearance of the membrane, and then to repeat the culture as long as necessary every fourth or fifth day. In 325 of these 752 cases the diphtheria bacilli disappeared within three days after the complete disappearance of the exudate; in 427 cases the diphtheria bacilli persisted for a longer time, viz: in 201 cases for 5 to 7 days; in 84 cases for 12 days; in 69 cases for 15 days; in 57 cases

for 3 weeks; in 11 for 4 weeks, and in 5 for 5 weeks. In a case recently communicated to the writer by Park the bacilli were found 7 weeks after disappearance of the membrane.

The virulence of the diphtheria bacilli after recovery is reported by Park in 14 cases, the bacilli being obtained at intervals of 10 to 44 days after the inception of the disease. Eight guinea-pigs died within 40 hours, and one in each of the following periods: 60-70 hours, 5 days, 8 days, 9 days, 11 days, and 14 days. One guinea-pig survived after extensive local necrosis. He concludes that the diphtheria bacilli which persist in the throat after an attack of diphtheria are always virulent for some time. In those exceptional cases in which the bacilli persist for a very long time they are found occasionally to lose their virulence a few days before their final disappearance, while in other cases they retain their virulence to the end. In one case the bacilli were virulent 8 weeks after the onset of the disease and 7 weeks after the disappearance of the membrane. That the cases themselves do not seem so liable to spread diphtheria is probably largely on account of the relatively small number of the bacilli in the convalescent throats, as compared with those showing the lesions of diphtheria. Reference has already been made to the rule of the Health Department to keep cases of diphtheria under supervision until the diphtheria bacilli have disappeared, and to practise disinfection as soon as they have vanished from the throat.

Park reports that thorough irrigation of the throat and nose with 1 to 4000 bichloride of mercury solution every few hours was attended by disappearance of the bacilli within three or four days after disappearance of the false membrane in from one-half to two-thirds of the cases. In the remaining cases the bacilli persisted from four to twenty days, notwithstanding the application of the bichloride solution. The duration of persistence of the bacilli with irrigation with simple salt-water was three days less than with bichloride irrigation.

Where cultures cannot be made it is recommended to continue the isolation of diphtheria patients for at least three weeks after the disappearance of the membrane.

Morse investigated twenty-five cases of diphtheria with reference to the length of time the diphtheria bacilli persist in the throat and nose. He found the average duration of their presence after disappearance of the membrane to be ten days, and this to be the same for both throat and nose, although they were found longer in the throat in some cases, and in the nose in others. The bacilli disappeared in one case the day after the throat was clear; in three, three days after, and in one, four days after. In two cases in which the bacilli were never found in the nose, they remained in the throat ten and seventeen days respectively. In other cases they were present: in the throat thirty-seven days, in

the nose thirty-six days; in the throat twenty-two days, in the nose eighteen days; in the throat ten days, in the nose seventeen days; and in both twenty-seven days. The bacilli obtained after ten days were found of usual virulence; in other cases of this group the virulence is not recorded. Patients are not permitted to leave the hospital until the diphtheria bacilli have disappeared from both throat and nose.

PRESENCE OF DIPHTHERIA BACILLI IN HEALTHY THROATS OF PERSONS EXPOSED TO DIPHTHERIA.—An interesting investigation has been carried out by Park to test the frequency with which the healthy throats of children contain diphtheria bacilli in families where a case of diphtheria exists and where little or no isolation is undertaken. The throats of fourteen families were investigated, in which there were forty-eight children. In 50 per cent. of these virulent diphtheria bacilli were found; 40 per cent. developed later, to a greater or less extent, the lesions of diphtheria. It is noted in Park's paper that, in these families, the conditions were the best possible for the transmission of the bacilli from one to the other. In families where the case of diphtheria was well isolated, the bacilli were found in less than 10 per cent. of the children.

The cases, as well as others to be mentioned presently, in which virulent diphtheria bacilli are found, sometimes in large number, in healthy throats of persons who do not develop diphtheria, prove that virulent diphtheria bacilli may be present in the throat and multiply there without causing any visible lesions. As has recently been pointed out with much clearness by Escherich, in order to cause diphtheria they must find susceptibility to their pathogenic action, which susceptibility may be local, or general, or both.

It is, for several reasons, of practical value to make bacteriological examinations of the healthy children's throats in families where diphtheria has developed, or who have been exposed to diphtheria, especially where isolation is defective. Experience has shown, as appears from Park's paper, that antiseptic irrigations and cleansing treatment of the throat in such cases greatly reduce the liability to develop diphtheria.

The dissemination of the disease is prevented by isolating those in whom the diphtheria bacilli are found. Doubtless, not a few cases of diphtheria of obscure causation are referable to those who without the symptoms and lesions of diphtheria carry about the virulent bacilli.

Park says: "All members of an infected household should be regarded as under suspicion, and in those cases where isolation is not enforced the healthy as well as the sick should be prevented from mingling with others until cultures or sufficient lapse of time give the presumption that they are not carriers of contagion."

For interesting illustrative cases and further details on this important matter, Park's paper should be consulted.

PRESENCE OF DIPHTHERIA BACILLI IN HEALTHY THROATS WHERE NO HISTORY COULD BE OBTAINED OF EXPOSURE TO DIPHTHERIA.—Park and Beebe examined the healthy throats of three hundred and thirty persons in New York who gave no history of direct contact with diphtheria. They found non-virulent, but otherwise characteristic, diphtheria bacilli in twenty-four, virulent characteristic diphtheria bacilli in eight, and non-virulent pseudo-diphtheria bacilli in twenty-seven. The virulence was tested by inoculating half-grown guinea-pigs with $\frac{1}{2}$ to 1 per cent. of their weight of forty-eight-hour bouillon cultures grown at body temperature. The non-virulent diphtheria bacilli produced acid in bouillon, and did not differ morphologically or in cultures from virulent diphtheria bacilli. Such bacilli are not regarded by Park as pseudo-diphtheria bacilli, but as genuine diphtheria bacilli devoid of virulence. The pseudo-diphtheria bacilli usually clouded bouillon and did not render it acid, and presented the usual characters of the pseudo-diphtheria bacilli to be described subsequently.

The non-virulent but otherwise characteristic diphtheria bacilli were abundant in the primary cultures from seventeen throats, and present in small number in the cultures from seven. In only one guinea-pig was there appreciable reaction after inoculation. Two hundred and eighty of the cases from which the cultures were made were children under twelve years of age (bacilli in twenty-two cases), while fifty were adults (bacilli in two). The non-virulent diphtheria bacilli persisted in four of the throats for four weeks, in one for three weeks, and in three for two weeks.

Of the eight cases in which virulent diphtheria bacilli were found, five were children in an asylum where from time to time cases of true diphtheria had occurred. Of the remaining three, one was from a house where a case of supposed croup had existed three weeks before. Two of the eight children developed diphtheria some days after making the cultures. The other six never developed any symptoms of diphtheria. The guinea-pigs inoculated with the cultures died in from twenty-eight to forty hours.

From the groups of cases studied under this and the preceding headings Park concludes that virulent diphtheria bacilli are present in probably about 1 per cent. of the healthy throats in New York City. Most of the persons in whose throats they exist have been in direct contact with cases of diphtheria. Many of those whose throats contain the virulent bacilli never develop diphtheria.

OCCURRENCE OF DIPHTHERIA BACILLI OUTSIDE OF THE HUMAN BODY.—In his first paper Park says that cultures made from the dried stains on spreads, pillow-cases, and sheets, where soiled by the expectoration of diphtheria patients, showed in every case a few colonies, at least, of the Loeffler bacillus. The sputum of patients, though apparently

free from bits of membrane, usually contained the bacilli in large number.

Important results have been obtained by Wright and Emerson, who have kindly furnished the writer an abstract of their unpublished work so far as it has yet been carried. They made cultures on blood-serum from the clothing, shoes, hair, and finger-nails of nurses in attendance on diphtheria patients, and also from the dust and various objects within the diphtheria ward of the Boston City Hospital. This ward contains seventy beds, which are generally nearly all occupied. The hygienic condition of the ward is stated to be good. Material, such as dust, etc., was collected for the most part on a sterilized platinum wire and applied to the surface of the culture medium. About twenty cultures in all have been made, of which five yielded Loeffler bacilli in small numbers. In all of the positive cases the bacilli isolated in pure culture were tested thoroughly as to their virulence and their morphological and cultural characters, and positively identified. In the latter respect all were characteristic diphtheria bacilli. It may be especially noted that all rendered bouillon acid within forty-eight hours. In two of the five cases the bacilli were of usual virulence, in two they were weakened in virulence, although killing guinea-pigs, and in one they caused only local reaction from which the animal recovered. The virulence was tested by inoculating guinea-pigs subcutaneously with $\frac{1}{2}$ to 1 per cent. of their weight of twenty-four- to forty-eight-hour bouillon cultures. From eight inoculated guinea-pigs which died, the characteristic bacilli were recovered in each instance, even when death occurred after some weeks.

The Loeffler bacilli were found on three shoes, each belonging to a different nurse, once on the hair of a nurse, the culture being taken from the hair above the ear, and once on a brush used in sweeping the floor of the ward.

The weakening of the virulence in two cases (in one case the guinea-pig died after seven and one-half days, and in another after some weeks, bacilli from each being recovered from the seat of inoculation) and the production of only slight local reaction from which the animal recovered in the case in which the bacilli were found on the hair of a nurse, suggest attenuation of virulence by unfavorable environment.

These suggestive observations of Wright and Emerson tell their own story and need no special comment.

No observations have been reported in this country of diphtheria as a spontaneous affection of domestic animals. Abbott was unable to confirm Klein's observations of the elimination of diphtheria bacilli through the milk of cows inoculated with virulent cultures of the Loeffler bacillus.

METHODS OF DISSEMINATION OF DIPHTHERIA.—How manifold may be the modes of conveyance of the diphtheria bacillus, and how

obscure and difficult or even impossible to trace may be the origin of some cases of diphtheria, is evident from observations which have been mentioned. Park from his rich experience summarizes and illustrates with interesting examples some of the ways in which the diphtheria germ may be transported.

Here we cannot do more than enumerate some of the sources of infection which have been established by bacteriological investigations, to wit: the pseudo-membranes, exudates and discharges of diphtheria patients, both those with typical diphtheria and those with mild and little characteristic forms of the disease; infected clothing, bedding, and other objects; occupying rooms where diphtheria has existed; convalescent or recovered cases in whom the diphtheria bacilli persist; persons who have been in contact with others having diphtheria bacilli on their persons or clothing, or with infected objects, such persons sometimes carrying diphtheria bacilli in their throats for days or weeks without lesion. The investigations of Wright and Emerson show on what varied objects the diphtheria bacilli may be carried. Park traced one group of cases of diphtheria to a candy-store kept by a family in which occurred a case of diphtheria. Children who bought candy at this store acquired diphtheria, and other children who came in contact at school with the healthy children of this family also developed diphtheria.

The investigations of the Health Department indicate that at present the whole tenement-house district of New York is an infected area. In plotting out on a map the distribution of cases of diphtheria in New York it was interesting to note two types of epidemics, one essentially of neighborhood infection, the other in which the cases could be attributed to infection at school. It was observed that a whole school district would suddenly become the seat of scattered cases. At times, in a certain area of the city from which several schools drew their scholars, all the cases of diphtheria would occur in families whose children attended one school, the children from the other schools being for a time exempt.

In about one-half of the cases of diphtheria in New York careful inquiry failed to show connection with other cases.

Influences which increase susceptibility to diphtheria doubtless play a rôle in determining the development of the disease. The majority of adults and many children are insusceptible. What these predisposing influences are we do not know, save the influence of age. That special local conditions, the presence of throat affections and the association of the diphtheria bacillus with other micro-organisms, particularly streptococci, are predisposing factors seems highly probable. It is also probable that the degree of virulence of the diphtheria bacillus and the number of bacilli received into the body must be taken into account.

We possess no evidence that the diphtheria bacillus finds a natural home outside of the human body, although it may survive for months on objects outside of the body. Park found living diphtheria bacilli on bits of membrane dried for seventeen weeks, and in blood-serum cultures seven months old.

PSEUDO-DIPHTHERIA BACILLUS.—The various questions relating to the pseudo-diphtheria bacillus have been investigated by Abbott, Koplik, and Park.

In fifty-three cases of various throat affections, mostly without suspicion of diphtheria, examined bacteriologically by Abbott, he found in three bacilli indistinguishable morphologically or in cultures from the Loeffler bacillus, but entirely devoid of virulence, as tested repeatedly on guinea-pigs. One of the cases was suspicious of diphtheria, there being a grayish membrane on the tonsils; one was a case of syphilitic pharyngitis without membrane, and the other was follicular tonsillitis. From a fourth case of this series with a grayish-white deposit on the tonsils, Abbott cultivated a bacillus resembling the Loeffler bacillus, but somewhat thicker, growing more luxuriantly on agar, clouding bouillon and growing visibly on potato, exceptionally invisibly. This bacillus was wholly non-pathogenic for guinea-pigs. As already mentioned, Abbott and his pupil, Ravenel, have found in two cases of membranous rhinitis bacilli indistinguishable from the Loeffler bacillus except that they failed to kill guinea-pigs, although producing local reaction.

Abbott's conclusion is that the diphtheria bacillus varies in its virulence and that non-virulent varieties of the bacillus occur. He says that the name pseudo-diphtheria bacillus should not be applied to those bacilli which possess all of the morphological and cultural characters of the Loeffler bacillus and are devoid of virulence. These are simply non-virulent diphtheria bacilli. He reserves the term pseudo-diphtheritic bacillus "for that organism or group of organisms (for there are probably several) that is enough like the diphtheria bacillus to attract attention, but is distinguishable from it by certain morphological and cultural peculiarities aside from the question of virulence."

Koplik does not seem to have met with a bacillus presenting all the morphological and cultural properties of the virulent diphtheria bacillus but devoid of virulence. He emphasizes the importance, in testing virulence, of observing the precautions especially signalized by Behring and by Escherich, as already mentioned, and gives examples showing that mistakes on this point can readily be made where old cultures and insufficient doses are used. Koplik has, however, in six cases out of a large number examined found the pseudo-diphtheria bacillus essentially as described by Hoffmann, and he would limit the name pseudo-diphtheria bacillus to the bacillus presenting these definite characters. This pseudo-diphtheria bacillus he describes in his first article as shorter and slightly

plumper than the real bacillus, but subsequently he describes it as an exact counterpart of the Loeffler bacillus in shape, size, and staining peculiarities, with the exception of deeper staining with methylene-blue. Actual measurements do not show any constant difference in thickness or length from the Loeffler bacillus. It grows upon blood-serum, potato, and gelatin, like the genuine bacillus. Upon agar the growth is always more luxuriant, thicker and whiter than that of the real bacillus. In alkaline peptone bouillon the pseudo-bacillus causes in twenty-four hours diffuse clouding with abundant deposit. The reaction remains distinctly alkaline. Koplik communicates to the writer an unpublished observation to the effect that if the pseudo-bacillus be cultivated in closed tubes of Pasteur pattern, from which the oxygen has been absorbed by pyrogallate of potassium, there is an abundant sediment with diffuse clouding of the bouillon, and in forty-eight hours the reaction is found to be acid. Neither aerobic nor the acid anaerobic cultures are lethal to guinea-pigs, even in enormous doses. Nor does the preparation of an animal for weeks by the injection of such repeated doses protect it from the effects of small doses of a fresh culture of the virulent bacillus. This was proved not only upon guinea-pigs, but also upon sheep and dogs. Koplik's first article is illustrated with beautiful photographs of the real and the false diphtheria bacilli in microscopical specimens and in cultures. It contains also a very satisfactory photograph of involution forms of the diphtheria bacillus.

The pseudo-bacillus was found by Koplik in four cases, already mentioned, with inflammation of the tonsils, without the real bacillus. In two cases of lacunar tonsillar diphtheria virulent typical diphtheria bacilli persisted in the crypts, in one case for three weeks, and in the other case for two weeks. At the end of these periods the virulent bacillus gave place to a non-virulent bacillus indistinguishable morphologically from the real bacillus, but presenting the cultural characters above described of the pseudo-bacillus, this bacillus being found abundantly in exactly the same situations in which the virulent bacillus previously existed. These non-virulent bacilli persisted in the tonsillar lacunæ up to the sixth week after the onset of the illness in one case. Koplik suggests the possibility that under the influence of the lymph and leucocytes of the tonsils, the virulent bacillus was transformed into the non-virulent form. He considers, however, the relationship between these two bacilli to be still an open question, but upon the whole he seems to be of the opinion that they are distinct species. When found, the pseudo-diphtheria bacilli were abundant in the cultures. Koplik's results may be said to be confirmatory of those of Escherich.

Park found, in 20 cases diagnosticated as diphtheria, the bacilli to be virulent in all, but in three of these cases the cultures from the first colony selected, although characteristic, were not virulent, while, from

other colonies in the same cases they were fully so. As already stated, Park used in testing virulence forty eight hours' broth cultures injected in doses of one-quarter to one-half or even one per cent. of the body-weight of the guinea-pig—selecting, where possible, young guinea-pigs. Park, therefore, confirms the observation of Roux and Yersin as to the possible coexistence of virulent and non-virulent bacilli in the same throat. He considers that in suspicious cases one should not be content with cultures from a single colony, if this should prove not to be virulent.

In this connection it may be mentioned that Park found no definite relation between the virulence of the cultures and the severity of the case. Nor was he able in an extended research to discover a relationship between the size of the bacillus and its virulence such as has been claimed by some investigators. He states that the results of 1613 cultures in which this factor was carefully noted in relation to the severity of the case indicate that in New York the great majority of cases of diphtheria yield in cultures bacilli of medium size which are characteristic in shape and in manner of staining, and that in a moderate number the bacilli are much longer, and in about an equal number they are much shorter. Both clinical histories and animal experiments showed that as long as in shape and staining the bacilli are characteristic, nothing as regards their virulence can be judged from their size. Those bacilli, on the other hand, which are short and stain uniformly with methylene-blue usually turn out to be of the pseudo-diphtheria type which have no virulence in animals.

It has already been mentioned that Park found exceptionally in cases in which diphtheria bacilli persisted in the throat a long time after recovery from diphtheria, attenuation of virulence to a point in which the cultures, although producing local reaction, failed to kill guinea-pigs.

We have cited already the investigations of Park and Beebe upon the healthy throats of 330 persons who gave no history of direct contact with diphtheria. In 24 of these they found bacilli indistinguishable from the diphtheria bacillus except by absence of virulence, which was tested by injecting forty-eight-hour broth cultures in doses of one-half to one per cent. of their weight into half-grown guinea-pigs. In 19 of these 24 cases the bacilli were grown in broth. In all of these the bacilli formed acid by their growth in forty-eight hours, sometimes more, sometimes less acid than control cultures of virulent bacilli. In 13 the broth culture was entirely characteristic, like that of the virulent bacillus, while in 6 the culture became more or less clouded, an effect which is exceptionally produced also by the virulent bacillus. No difference was found as to the growth on blood-serum. Upon agar the growth was typical of that of the virulent bacillus in 11 cases, while from 7 the bacilli grew in a less typical manner, but always in ways seen occasionally with the virulent form. Of the guinea-pigs inoculated with cultures from 15 of the cases,

in only one was there any appreciable local reaction, and this subsided within four days. A very slight degree of immunity seemed to be afforded to some of the guinea-pigs by the injection.

In 27 cases the pseudo-diphtheria bacillus, which, as well as the genuine diphtheria bacillus, has been most satisfactorily photographed in cover-slip specimens and cultures by Park, was found presenting in general the characters described above. Park describes this bacillus as shorter and thicker and more uniform in size and staining than the virulent Loeffler bacillus. It clouded and formed alkali in bouillon in the first forty-eight hours, grew more luxuriantly on agar, and was not pathogenic. Park would confine the name pseudo-diphtheria bacillus to the bacillus or group of bacilli presenting these general characters.

Park, as well as Abbott, therefore, recognizes a non-virulent form of the diphtheria bacillus, and contends that bacilli indistinguishable from the diphtheria bacillus except by absence of virulence, should not be called pseudo-diphtheritic. He admits certain morphological and cultural variations of the true diphtheria bacillus, such as variations in size, occasional clouding of bouillon, exceptional luxuriance of growth on serum and agar, etc., but the production of acid in bouillon he regards as essential to the diagnosis of the diphtheria bacillus.

The pseudo-diphtheria bacillus, as defined above, is regarded by Park as a species distinct from the genuine diphtheria bacillus, either in its virulent or its non-virulent state. Park calls attention to the confusion introduced into the discussions on the pseudo-diphtheria bacillus by the fact that some have given this name to bacilli indistinguishable from the diphtheria bacillus except by absence of virulence, whereas others have worked with the genuine pseudo-diphtheria bacillus, which presents cultural and morphological differences from the genuine diphtheria bacillus.

It would seem to be established, therefore, by the investigations of Abbott and Park, that a bacillus in no way distinguishable from the diphtheria bacillus except by absence of virulence exists. Although other investigators have included this non-virulent but otherwise characteristic diphtheria bacillus under the designation pseudo-diphtheria bacillus, they contend that this name is inappropriate for this bacillus, which should be considered as the genuine diphtheria bacillus, which may present all degrees of virulence down to complete harmlessness, as tested on guinea-pigs. This non-virulent bacillus has been found only in a comparatively small number of cases, these cases being chiefly without characteristic lesions of diphtheria. Occasionally the virulent and the non-virulent diphtheria bacilli are found side by side in diphtheria, and occasionally the virulent bacillus has given place to the non-virulent bacillus during or after recovery from diphtheria.

Abbott, Koplik, and Park would limit the name pseudo-diphtheria bacillus to bacilli which, although bearing resemblance to the diphtheria

bacillus, differ from it not only by absence of virulence toward guinea-pigs but also by cultural characteristics.

Abbott considers that there is a group of bacteria which in this sense may be called pseudo-diphtheritic, and that they are distinct species from the diphtheria bacillus. Koplik describes with much detail a special bacillus observed by him in six cases, which he considers to be identical with the original pseudo-diphtheria bacillus of Hoffmann, and to which he would limit the name pseudo-diphtheria bacillus. This bacillus grows on agar more luxuriantly than the genuine diphtheria bacillus, and it does not change the reaction of alkaline glucose bouillon in aerobic cultures, although it produces acid in anaerobic cultures. While not expressing a positive decision, he seems inclined to regard this bacillus as distinct in species from the genuine diphtheria bacillus.

Park has probably worked with the same bacillus, at least the same as the one described by Koplik in his first article, and he also would limit the name pseudo-diphtheria bacillus to this bacillus, or to a group of bacilli presenting these several characteristics, if, as is probable, such a group exists. He considers that this bacillus, or these bacilli, differ from the genuine diphtheria bacillus at least as much as the colon bacillus differs from the typhoid bacillus. The pseudo-diphtheria bacillus was found in only a small number of cases out of the many examined, and appeared to have nothing to do with diphtheria.

SUMMARY.—This paper is a report of the results of the bacteriological study of diphtheria in the United States up to May, 1894, so far as these results are of interest for the purposes of this Congress. The investigations were made by various men in New York, Baltimore, Boston, and Philadelphia.

Some of the more important conclusions may be summarized as follows:

1. The Health Department of New York has undertaken the bacteriological examination of all cases of suspected diphtheria in that city, unless objection is made by the attending physician or unless it is not deemed advisable to disturb the patient by such examination. The methods employed are described in detail. During the year ending May 4, 1894, cultures were made from 5611 cases of suspected diphtheria. The results have proven satisfactory, and are utilized not only for diagnosis, but also to control the supervision and isolation of the cases.

2. Of 6156 cases of suspected diphtheria in New York and Boston, 58½ per cent. were proven bacteriologically to be true diphtheria—or, if we include only those cases in which the bacteriological examination was considered to be entirely satisfactory—of 5340 cases, 67½ per cent. were true diphtheria. These were pseudo-membranous inflammations

of the throat and air-passages uncomplicated for the most part with scarlet fever.

3. At least 80 per cent. of the cases of membranous croup in New York were diphtheria, and only 14 per cent. were shown not to be diphtheria.

4. Fifteen cases of fibrinous rhinitis and 4 cases of primary and exclusively nasal diphtheria were all due to the diphtheria bacillus.

5. Various forms of atypical diphtheria, many without membrane, and with the characters of simple catarrhal angina and follicular tonsillitis, are described.

6. Instances of unusual localizations of the diphtheria bacillus, as in the middle ear, in wounds, ulcers, abscesses, conjunctivæ, lungs, heart-valves, and the distribution of the bacilli at autopsies of human beings and of guinea-pigs dead of diphtheria, are described.

7. The various bacteria found associated with the diphtheria bacillus, the most important pathogenic forms being streptococci, staphylococci, and the diplococcus lanceolatus, are considered.

8. In general the great majority of cases of pseudo-membranous anginas in scarlet fever are due to streptococci, but where diphtheria is prevalent and opportunities are favorable for exposure to diphtheria a large proportion may be due to the diphtheria bacillus. The statistics in Baltimore and in Boston present interesting contrasts in illustration of this point. Four cases of diphtheria complicating typhoid fever are described.

9. The name pseudo-diphtheria is applied to pseudo-membranous inflammations of the throat and air-passages not caused by the diphtheria bacillus. The most important and common micro-organism in pseudo-diphtheria is the streptococcus pyogenes, but other bacteria may be the cause. The mortality in these affections is low in private practice, being 1.7 per cent. in 408 consecutive cases in New York. In hospitals it may be as high as 25 per cent. Death is generally due to some complication, the most important complications being scarlet fever, membranous laryngitis, and broncho-pneumonia. The disease seems to be only slightly, if at all, contagious. For this reason, and on account of the low mortality in uncomplicated cases, those cases which are proved bacteriologically not to be true diphtheria are not kept under supervision by the Health Department in New York. Until such proof suspicious cases are treated as diphtheria.

10. Of 752 cases of diphtheria in New York, the diphtheria bacilli in 325 disappeared within three days after the complete disappearance of the exudate. In 427 cases the bacilli persisted for a longer time, viz., in 201, for from five to seven days; in 84, for twelve days; in 69, for fifteen days; in 57, for three weeks; in 11, for four weeks; and in 5, for five weeks. In one case, virulent bacilli were found seven weeks after

disappearance of the exudate. The cases are kept under supervision until the bacilli have disappeared. Sometimes they disappear first from the nose; at other times, first from the throat.

11. In fourteen families, with forty-eight children, where little or no isolation of a case of diphtheria in each family was undertaken, virulent diphtheria bacilli were found in 50 per cent. of the children, of whom 40 per cent. later developed diphtheria. The bacilli were found in less than 10 per cent. of the children in families where the case of diphtheria was well isolated.

Antiseptic irrigation and cleansing treatment of the throat lessens the liability of those thus exposed to develop diphtheria.

All members of an infected household should be regarded as under suspicion, and where isolation is not enforced the healthy as well as the sick should be prevented from mingling with others until cultures or sufficient lapse of time give the presumption that they are not carriers of contagion.

12. Diphtheria bacilli may be present and multiply in the throat without causing symptoms or lesions. They must find susceptibility to their pathogenic action in order to cause diphtheria.

13. In three hundred and thirty persons who gave no history of direct contact with diphtheria, virulent diphtheria bacilli were found in eight, of whom only two subsequently developed diphtheria. Bacilli, indistinguishable morphologically or in cultures from the diphtheria bacillus, including the formation of acid in forty-eight hours in bouillon, but entirely devoid of virulence, were found in twenty-four of these persons, in most of these instances in large numbers. The pseudo-diphtheria bacillus was found in twenty-seven.

14. Instances are given in which the diphtheria bacilli were found on various objects outside of the human body, viz., bed-clothing soiled with discharges of diphtheria patients; the shoes and the hair of nurses in attendance on diphtheria patients, and a brush used in sweeping the floor of a diphtheria ward.

15. Some of the various ways in which the diphtheria germ is transported are summarized.

16. A bacillus in no way distinguishable in morphology or in cultures, including the formation of acid in bouillon, from the usual diphtheria bacillus, but devoid of virulence, exists. The virulence was tested by injecting into half-grown guinea-pigs $\frac{1}{2}$ to 1 per cent. of their weight of forty-eight-hour bouillon cultures. This bacillus, although it has been called by some investigators the pseudo-diphtheria bacillus, should not be so designated. It is the genuine diphtheria bacillus devoid of virulence. It was met with in a comparatively small number of cases out of a large number examined. Exceptionally, it may occur together with the virulent diphtheria bacillus in diphtheria, and occasionally it

takes the place of the virulent bacillus during or after recovery from diphtheria. In several instances it was found in healthy throats.

The name pseudo-diphtheria bacillus should be confined to bacilli which, although resembling the diphtheria bacillus, differ from it not only by absence of virulence, but also by cultural peculiarities, the most important of the latter being greater luxuriance of growth on agar and the preservation of the alkaline reaction of bouillon cultures. The pseudo-diphtheria bacillus may render bouillon cultures acid in forty-eight hours when grown anaerobically. The pseudo-diphtheria bacillus in this sense was found in a number of cases, but not frequently. It is probably of different species from the genuine diphtheria bacillus, and is without diagnostic importance.

ARTICLES CITED IN THE TEXT.

Abbott, A. C.: The Relation of the Pseudo-Diphtheritic Bacillus to the Diphtheritic Bacillus. Bulletin of the Johns Hopkins Hospital, August, 1891.

— Further Studies upon the Relation of the Pseudo-Diphtheritic Bacillus to the Diphtheritic Bacillus. Bulletin of the Johns Hopkins Hospital, October-November, 1891.

— The Etiology of Membranous Rhinitis (Rhinitis Fibrinosa). The Medical News, May 13, 1893.

— The Results of Inoculations of Milch Cows with Cultures of the Bacillus Diphtheriæ. The Journal of Pathology and Bacteriology, October, 1893.

— and *Ghriskey, A. A.*: A Contribution to the Pathology of Experimental Diphtheria. Bulletin of the Johns Hopkins Hospital, April, 1893.

Booker, William D.: The Relation of Pseudo-Diphtheritic Angina to Diphtheria, with special reference to Scarlatinal Pseudo-Membranous Angina. Bulletin of the Johns Hopkins Hospital, October-November, 1892.

— As to the Etiology of Primary Pseudo-Membranous Inflammation of the Larynx and Trachea, with Remarks on the Distribution of the Diphtheria Bacilli in Organs of the Body Distal from the Seat of Local Infection. Transactions of the American Pediatric Society, vol. v.

Councilman, W. T.: The Pathology and Diagnosis of Diphtheria. THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, November, 1893.

Fleener, Simon: Diphtheria with Broncho-Pneumonia. Bulletin of the Johns Hopkins Hospital, April, 1893.

Howard, W. T., Jr.: Acute Ulcerative Endocarditis due to the Bacillus Diphtheriæ. Bulletin of the Johns Hopkins Hospital, April, 1893.

Johnston, Wyatt: A New Method for the Culture of Diphtheria Bacilli in Hard-boiled Eggs. The Medical News, December 10, 1892.

Koplik, Henry: Forms of True Diphtheria which Simulate Simple Catarrhal Angina. The New York Medical Journal, August 27, 1892.

— Acute Lacunar Diphtheria of the Tonsils, with Studies on the Relation of the Real to the Pseudo-Bacillus Diphtheriæ. The New York Medical Journal, March 10, 1894.

Morse, John Lovell: A Bacteriological Study of Four Hundred Cases of Inflammation of the Throat, occurring in Diphtheria and Scarlet Fever, with Especial Reference to Pathogenesis. The Boston Medical and Surgical Journal, February 15 and 22, 1894.

Park, William Halleck: Diphtheria and Allied Pseudo-membranous Inflammations. A Clinical and Bacteriological Study. The Medical Record (New York), July 30 and August 6, 1892.

— Diphtheria and other Pseudo-membranous Inflammations. A Clinical and Bacteriological Study. Second Paper. The Medical Record, February 11, 1893.

— The unpublished manuscript of a report to the Board of Health of New York contains a large part of the observations of Park cited in the text. The examinations for bacteriological diagnosis in suspected cases of diphtheria reported in this paper were made by Dr. Park in about two-thirds of the cases and by Mr. Alfred Beebe in about one-third. This manuscript, which was prepared in part for this report to the Congress, has been kindly placed at the disposal of the writer.

Prudden, T. Mitchell: On the Etiology of Diphtheria. An Experimental Study. AMER. JOURN. OF THE MEDICAL SCIENCES, April and May, 1889.

— Studies on the Etiology of Diphtheria. Second series. The Medical Record, April 18, 1891.

Ravenel, M. P.: Notes on Two Cases of Membranous Rhinitis (unpublished manuscript).

Townsend, Charles W.: Primary Nasal Diphtheria. The Boston Medical and Surgical Journal, May 24, 1894.

Welch, William H.: The Causation of Diphtheria. Transactions of the Medical and Chirurgical Faculty of Maryland, 1891.

— and *Abbott, A. C.*: The Etiology of Diphtheria. Bulletin of the Johns Hopkins Hospital, February and March, 1891.

— and *Flexner, Simon*: The Histological Changes in Experimental Diphtheria. Bulletin of the Johns Hopkins Hospital, August, 1891.

— The Histological Lesions Produced by the Toxalbumin of Diphtheria. Bulletin of the Johns Hopkins Hospital, March, 1892.

Woods, Hiram: Diphtheritic Conjunctivitis: Report of Two Cases, with the Bacteriologic Study of the False Membrane. The Medical News, August 20, 1892.

Wright, J. H.: Manuscript of unpublished work on Diphtheria sent to the writer of this report.

— and *Emerson, H. C.*: On the Occurrence of the Bacillus Diphtheriæ outside of the Body (unpublished manuscript prepared for this report).

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