ing muscular energy. In overdose they cause in dogs and guinea-pigs convulsions, reduction of the hæmoglobin, and blackish urine. *W. A. Bastedo.*

DIPHTHERIA.—History.—The specific contagious disease which we now call diphtheria, and, therefore, according to our present belief, the bacilli which cause it, can be traced back to almost the Homeric period of Grecian history. The Greeks believed that it had been communicated to their country from Egypt. The description of the pharyngeal and laryngeal manifestations of this disease left by Aretæus leaves no doubt that it was of diphtheria that he wrote. Galen, in his remarks on the Chironian ulcer, tells us that the pseudo-membrane was gotten rid of by coughing in the laryngeal form of the disease, and by hawking in the pharyngeal type. From time to time during the next one thousand years we hear of epidemics both in Italy and in other portions of the civilized world. In 1517 we read of a malignant form of the disease raging in Switzerland, along the Rhine, and in the Netherlands. The disease now crossed to America, and in the New England States we get clear accounts of its ravages. Thus, Samuel Danforth, in 1659, lost four of his eleven children within a fortnight by a "malady of the bladders in the windpipe." In 1765, Home, a Scotchman, tried to show that "croup" and pharyngeal diphtheria were different diseases, or, in bacteriological terms, due to different micro-organisms, and this subject remained under controversy until it was recently settled that while most cases were undoubtedly true diphtheria, a few were not.

Bard, an American, supported, in 1771, the opposite theory from Home, considering the process the same wherever located. In this ground he was much nearer to the facts than Home. His observations upon diphtheria were very important and accurate.

In 1821, Bretonneau published his first essay on diphtheria in Paris and gave to the disease its present name. His observations were so extensive and so correct that little advance in knowledge took place until the causal relations of the diphtheria bacilli and their associated micro-organisms to the disease began to be recognized. Since then the combined clinical, bacteriological, and pathological studies have sufficed to make diphtheria one of the best understood of diseases.

Bacteriology.—*The Bacillus of Diphtheria.*—In the year 1883 bacilli which were very peculiar and striking in appearance were shown by Klebs to be of constant occurrence in the pseudo-membranes from the throats of those dying of true epidemic diphtheria. One year later, Löffler published the results of a very thorough and extensive series of investigations on this subject. He found the bacillus described by Klebs in many cases of throat inflammations which had been diagnosticated as diphtheria. When he inoculated the bacilli upon the abraded mucous membrane of susceptible animals, more or less characteristic pseudo-memberranes we produced, and frequently death or paralysis followed, with characteristic lesions.

All the conditions have since then been fulfilled for diphtheria which are necessary to the most rigid proof of the dependence of an infective disease upon a given micro-organism—viz., the constant presence of this organism in the lesions of the disease, the isolation of the organism in pure culture, the reproduction of the essential lesions of the disease in animals and in man by inoculation with pure cultures, the failure to produce all the characteristic lesions of this disease by any other bacteria, and the additional proof of the immunizing value of the specific substances developed in animals subjected to injections of diphtheria toxin. In view of these facts we are now justified in saying that the name diphtheria, or at least primary diphtheria, should be applied, and exclusively applied, to that acute infectious disease usually associated with pseudo-membranous affection of the mucous membranes which is primarily caused by the Bacillus diphtheriæ of Löffler. Other bacteria do, indeed, occasionally produce local lesions which simulate in one way or another those caused by the diphtheria bacillus, but none of them ever produce lesions similar in their totality to those of a characteristic case of diphtheria. As the diphtheria bacilli have been quite fully described in Vol. I., p. 694, only those points will be given here which need to be more fully stated, on account of their important relations to diagnosis and treatment.

The Klebs-Löffler bacilli *stain* readily with ordinary aniline dyes, and retain fairly well their color after staining by Gram's method. When Löffler's alkaline solution of methylene blue is applied cold for five minutes or warm for one minute the bacilli from blood-serum cultures especially, and from other media less constantly, stain in an irregular and extremely characteristic way. Many of the bacilli do not stain uniformly. In many cultures round or oval bodies situated at the ends or in the central portions stain much more intensely than the rest of the bacillus. These bodies have been shown by Williams to bear much the same relations to the bacilli as nuclei do to cells. In old cultures the bacilli stain poorly and not at all in a characteristic way. The same round or oval bodies which take the methylene blue more intensely than the remainder of the bacillus are brought out still more distinctly by the Neisser stain. (See Vol. I., Plate X., Fig. 4, and page 695.)

The Neisser stain has been advocated in order to separate the virulent from the non-virulent bacilli without the delay of inoculating animals; but in our hands, with a very large experience, neither the Neisser stain nor any other stain is capable of doing this, and none appear to me to give any more information as to the virulence of the bacilli than the usual methylene-blue solution of Löffler. A small percentage of virulent bacilli fail to take the Neisser stain, and quite a few non-virulent pseudo-diphtheria bacilli show the dark bodies. In New York there are also a large number of bacilli which seem to have all the staining and cultural characteristics of the virulent bacilli, and yet are non-virulent in the sense that they produce no specific toxin. The Neisser stain will undoubtedly cause the examiner to suspect more strongly some bacilli of being virulent than the Löffler stain, but with the varieties met with in New York this suspicion is as apt to be wrong as right. Nothing but the animal inoculations with control injections of antitoxin will separate specifically virulent from non-virulent bacilli.

Biology.—The Klebs-Löffler bacillus does not form spores. Its thermal death point with ten minutes' exposure is about 58° C., and with longer exposure a lower temperature; it is more easily destroyed by disinfectants than are many other bacteria. In the dry state and exposed to diffuse light diphtheria bacilli usually die in a few days but occasionally may live for weeks or months; when in the dark, or protected by a film of mucus or albumin, they may live for even longer periods. The bacillus is not sensitive to cold, for I found it to retain its virulence after exposure for two hours to several hundred degrees below zero. It begins to develop, but grows slowly, at a temperature of 20° C., or even less. It grows more rapidly as the temperature rises, and attains its maximum development at 37° C.

The growth of the diphtheria bacillus upon agar presents certain peculiarities which are of practical importance in connection with cultures for diagnosis. If a large number of the bacilli from a recent culture are implanted upon a properly prepared agar plate, a certain and fairly vigorous growth will always take place. If, however, the agar is inoculated with an exudate from the throat which contains but few bacilli, no growth whatever may occur, while the tubes of coagulated blood serum inoculated with the same exudate contain the bacilli abundantly. Because of the uncertainty, therefore, agar is a far less reliable medium than blood serum for use in primary cultures for diagnostic purposes.

Growth in Ascitic Bouillon: Diphtheria bacilli can almost be divided into two great groups: one growing readily in bouillon, while the other scarcely grows at all when first removed from the throat. All varieties, however, develop luxuriantly when to the bouillon twenty-

five per cent. ascitic fluid or blood serum is added. Lately this fact has been made use of with great success in getting pure cultures of diphtheria bacilli from throat cultures when virulence tests are desired. The ascitic bouillon is inoculated with the mixed bacteria from the original culture from the throat; after twenty-four or forty-eight hours a pellicle will develop if any diphtheria bacilli were present in the material inoculated. This pellicle will be found to be composed almost wholly of diphtheria bacilli. Plate cultures are then made and the bacilli readily isolated.

Growth in Milk: The diphtheria bacillus grows readily in milk, beginning to develop at a comparatively low temperature (20° C.). Thus milk having become inoculated with the bacillus from some cases of diphtheria may under certain conditions be the means of conveying infection to previously healthy persons. Though this growth takes place, the milk remains unchanged in appearance.

Pathogenesis.—The diphtheria bacillus is pathogenic for guinea-pigs, rabbits, chickens, pigeons, small birds, and cats; also in a lesser degree for dogs, goats, cattle, and horses, but hardly at all for rats and mice. In spite of its pathogenic qualities for these animals true diphtheria occurs in them with extreme rarity. I have met with one cat which had typical diphtheria and from which the diphtheria bacilli were isolated and proved virulent. As a rule, supposed diphtheritic inflammations in them are due to other bacteria which cannot produce the disease in man.

The virulence of diphtheria bacilli from different sources, as measured by their toxin production, may vary enormously. Thus 0.002 c.c. of a forty-hour bouillon culture of one bacillus will kill a guinea-pig, while it would require 1 c.c. of the culture of another bacillus to kill. From well-marked cases in New York, however, the bacilli have as a rule about the same virulence, nor did they lose in virulence to any great extent when they persisted in the throat secretions after convalescence. The same marked variation occurs in the amount of toxin produced by different bacilli in their growth in media outside of the body. There are also bacilli which produce no specific toxin whatever and yet appear to have all the other characteristics of virulent bacilli.

Diphtheria Toxin.—It is evident that a micro-organism which, when injected subcutaneously, destroys the life of susceptible animals and produces such marked anatomical changes in the internal organs, while it is found only at or near the point of inoculation, must owe its pathogenic power to the formation of a poison which, being absorbed, gives rise to toxæmia and death. This poison or *toxin* has been partially isolated by Roux and Yersin, and others, by filtration through porous porcelain from cultures of the living bacilli. It has not yet been successfully analyzed, so that its chemical composition is unknown, but it has many of the properties of proteid substances, and can well be designated by the term active proteid.

Non-Virulent Diphtheria Bacilli.—In the very large number of tests for virulence of the bacilli obtained from hundreds of cases of suspected diphtheria which have been carried out during the past six years in the laboratories of the Health Department of New York City, in over ninety-five per cent. of cases the bacilli derived from exudates or pseudo-membranes and possessing the characteristics of the Löffler bacilli have been found to be virulent, that is, producers of diphtheria toxin. But there are, however, in inflamed throats as well as in healthy throats, either alone or associated with the virulent bacilli, occasionally bacilli, which, though morphologically and in their behavior on culture media identical with the Klebs-Löffler bacillus, are yet producers, at least in artificial culture media and the usual test animals, of no appreciable diphtheria toxin. Between bacilli which produce a great deal of toxin and those which apparently produce none we find all grades of virulence. So far as we know, bacilli which produce no specific toxin have never later been found to develop it. Bacilli are also found which resemble diphtheria bacilli very closely (except in toxin production), but differ in one or more particulars. Both these and the characterisic non-virulent bacilli are found occasionally upon all the mucous membranes, both when inflamed and when apparently normal.

Virulent bacilli produce and are found not only in pseudo-membranous inflammations of the fauces, larynx, and nasal cavities, but also occasionally in membranous affections of the skin, vagina, rectum, conjunctiva, nose, and ear (simple membranous rhinitis and otitis media). From the severity of an isolated case the virulence of the bacilli cannot be determined. The most virulent bacillus I have ever found was obtained from a mild case of diphtheria simulating tonsillitis. Another case, however, infected by this bacillus proved to be very severe. In localized epidemics the average severity of the cases probably indicates roughly the virulence of the bacillus causing the infection, as here the individual susceptibility of the different persons infected would, in all likelihood, when taken together, be similar to that of other groups; but even in this instance special conditions of climate, food, race, or concurrent infections may influence certain localities. Moreover, the bacteria associated with the diphtheria bacilli, and which are liable to be transmitted with them, may influence the severity of and the complications arising in the cases.

Virulent Bacilli in Healthy Throats.—Fully virulent bacilli have frequently been found in healthy throats of persons who have been brought in direct contact with diphtheria patients or infected clothing without contracting the disease. It is therefore apparent that infection in diphtheria, as in other infectious diseases, requires not only the presence of virulent bacilli, but also a susceptibility to the disease, which may be inherited or acquired. Among the predisposing influences which contribute to the production of diphtheritic infection may be mentioned the breathing of foul air and living in overcrowded and ill-ventilated rooms, poor food, certain diseases, more particularly catarrhal inflammations of the mucous membranes, and depressing conditions generally. Under these conditions an infected mucous membrane may become susceptible to disease. In connection with Beebe (1894) I made an examination of the throats of 330 healthy persons who had not come in contact, so far as known, with diphtheria, and we found virulent bacilli in 8 only, 2 of whom later developed the disease. In 24 of the 330 healthy throats non-virulent bacilli or attenuated forms of the diphtheria bacillus were found. Very similar observations have been made by others in many widely separated countries.

The Persistence of Diphtheria Bacilli in the Throat.—The continued presence of virulent diphtheria bacilli in the throats of patients who have recovered from the disease, and after the disappearance of the exudate, has been repeatedly demonstrated. Beebe and I found that in 304 of 605 consecutive cases the bacilli disappeared within three days after the disappearance of the pseudo-membrane; in 176 cases they persisted for seven days, in 64 cases for twelve days, in 36 cases for fifteen days, in 12 cases for three weeks, in 4 cases for four weeks, and in 2 cases for nine weeks. Since then I have met with a case in which they persisted for six months.

Mixed Infection in Diphtheria.—Virulent diphtheria bacilli, however, are not the only bacteria present in human diphtheria. Various cocci, more particularly streptococci, staphylococci, and pneumococci, are almost always found associated with Löffler bacilli in diphtheria, playing an important part in the disease and leading often to serious complications (sepsis and broncho-pneumonia). Indeed, the prognosis in a case of diphtheria is now judged to be graver, other things being equal, according to the degree in which other pathogenic bacteria influence the course of the disease. These cases of so-called *mixed infection* in diphtheria have within recent years attracted considerable attention, and have been the subject of a number of animal experiments. Though the results of these investigations so far have been somewhat

indefinite, they would seem to indicate that when other bacteria are associated with the diphtheria bacilli they mutually assist one another in their attacks upon the mucous membrane, the streptococcus being particularly active in this respect, often opening the way for the invasion of the Löffler bacillus into the deeper tissues or supplying needed conditions for the development of its toxin. Thus diphtheria is not always a primary, but often a secondary disease, following some other infection, as measles or scarlet fever. In most fatal cases of broncho-pneumonia following laryngeal diphtheria we find not only abundant pneumococci or streptococci in the inflamed lung areas, but also in the blood and tissues of the organs. As these septic infections due to the pyogenic cocci are in no way influenced by the diphtheria antitoxin, they frequently are the cause of the fatal termination. Other bacteria cause putrefactive changes in the exudate, producing alterations in color and offensive odors.

Pseudo-membranous Exudative Inflammations due to Bacteria other than the Diphtheria Bacilli.—The diphtheria bacillus, though the most usual, is not the only microorganism that is capable of producing pseudo-membranous inflammations. There are numerous bacteria present almost constantly in the throat secretions which, under certain conditions, can cause local lesions very similar to those in the less marked cases of true diphtheria. The streptococcus and pneumococcus are the two forms most frequently found in these cases, but there are also others which, under suitable conditions, take an active part in producing this form of inflammation. Some of these bacteria do not develop on artificial media, so that we know little of their characteristics. Among these is a long, slender bacillus which is occasionally found in great abundance in the middle layers of pseudo-membranes when the diphtheria bacillus is absent. This, or one similar to it, has been described by Vincent.* It does not grow on artificial media and is not pathogenic in animals. From its presence in the false membrane of a number of cases, it is believed to have some causal relation to them.

These cases show most of the local appearances of true diphtheria: the superficial necrosis of the epithelium, the membrane, and the glandular swellings. The pseudo-membranes may persist for from one to two weeks, or even, in exceptional cases, longer. This bacillus is apparently frequently present in the normal throat, and is probably only under certain favoring conditions, such as syphilis, able to produce lesions. Nerve degeneration and paralysis do not follow an attack.

The pseudo-membranous angina accompanying scarlet fever, and to a less extent other diseases, may show the presence not of diphtheria bacilli, but only of the pyogenic cocci, especially streptococci, or, more rarely, some varieties of little known bacilli. The deposit covering the inflamed tissue in these non-specific cases is, it is true, usually but not always, rather an exudate than a true pseudo-membrane. The majority of these cases, however, are mild affections, being of importance only in adding to the severity of the disease which they complicate. An exception should be made when the larynx is affected, as here the lungs are often secondarily involved. The bacteria which occur in *false diphtheria* are streptococci, staphylococci, diplococci, and sometimes pseudo-diphtheria bacilli or bacilli which are morphologically and culturally distinct from the Löffler bacilli. These will be referred to further under their respective organisms.

The Transmission of Diphtheria.—The possibility of the transmission of diphtheria from animals to man cannot be disputed, for cats and many animals can be infected, but, so far as I know, there are no authentic cases of such transmission on record. So-called diphtheritic disease in animals and birds is usually due to other micro-organisms than the diphtheria bacilli. Diphtheritic infection, however, can generally be traced, directly or indirectly, to its source; though there are undoubtedly some cases of diphtheria in which we cannot determine the source of the infection, for we have no reason to believe that diphtheria is ever spontaneous.

Let us consider some of the means by which the disease may be communicated. In actual experiment the bacilli have been observed to remain virulent in bits of dried membrane by Löffler for fourteen weeks, by us for seventeen weeks, and by Roux and Yersin for twenty weeks. Dried on silk threads Abel reports that they may sometimes live one hundred and seventy-two days, and upon a child's plaything which had been kept in a dark place they lived for five months. The virulent bacilli have been found on soiled bedding or clothing of a diphtheria patient, on drinking-cups, shoes, hair, slate pencils, etc. Beside these sources of infection by which the disease may be indirectly transmitted, virulent bacilli may be directly received from the pseudo-membrane, exudate, or discharges of diphtheria patients; from the secretions of the nose and throat of convalescent cases of diphtheria in which the virulent bacilli persist; and from the healthy throats of individuals who acquired the bacilli from being in contact with others having virulent germs on their persons or clothing. In such cases the bacilli may sometimes live and develop for days or weeks in the throat without causing any lesion. When we consider that it is only the severe types of diphtheria that remain isolated during their actual illness, the wonder is not that so many, but that so few, persons contract the disease. It indicates that very frequently virulent bacilli are received into the mouth, and then either find no conditions there suitable for their growth or are swept away by food or drink before they could effect a lodgment.

Susceptibility to and Immunity against Diphtheria.—An individual susceptibility, both general and local, to diphtheria, as in all infectious diseases, is necessary for the contraction of this disease. Moreover, the diphtheria poison does not produce the same effect on the mucous membranes of all persons. Age has long been recognized to be an important factor in diphtheria. Children within the first six months of life are but little susceptible, the greatest degree of susceptibility being between the third and the tenth years, while adults are almost immune. An inherited susceptibility or "family predisposition" to the disease has also been observed.

Long before the discovery of the Klebs-Löffler bacillus it was a well-known fact that two attacks of diphtheria seldom occurred in the same individual within short periods of time, and none of us would fear to leave a convalescent case in the same room with one still suffering from the disease. To what this natural susceptibility or immunity is due is still only partially understood, but, as the result of animal experiments, it is now known that an artificial immunity against diphtheria can be produced, at least for a considerable length of time, by the development of substances directly antidotal to the diphtheria toxin. By the inoculation of virulent or somewhat attenuated cultures or of diphtheria toxin, Fraenkel, Behring, Wernicke, Aronson, Roux, and since then many others, have succeeded in immunizing animals; but the most important and valuable results are those which have been obtained by Behring, in conjunction with others, who showed that the blood of immune animals contains a substance which neutralizes the diphtheria toxin. The blood serum of persons who have recovered from diphtheria has been found also to possess this protective property, which it acquires about a week after the beginning of the disease, and loses again in a few weeks or months. Moreover, the blood serum of many individuals, usually adults, who have never had diphtheria often has a slight general antitoxic property.

Antitoxin Serum.—The knowledge derived from these remarkable investigations into the protective powers of the blood serum of immunized animals has been employed with the most brilliant results for the prevention and early treatment of diphtheria in man. For the methods employed to obtain diphtheria antitoxic serum see Vol. I., page 698.

* Annales de l'Institut Pasteur, August, 1899.

Pathology.—*Location of Bacilli in the Membrane.**—We have never found the diphtheria bacilli growing in the living tissue, or in connection with those degenerative lesions in the epithelium which can be regarded as the primary lesions of the disease. They were found in the necrotic tissue and in the exudation, usually only in the latter. In a very few cases the bacilli were found enclosed in pus and in necrotic epithelial cells. They were nearly always found in clumps and masses. The masses found deep down in the membrane probably do not represent a downward growth in this, but have been covered up by a further formation of membrane on the surface. The diphtheria bacillus shows in its growth an affinity for solid structures, and is found rather on the reticulum than in the spaces between.

Usually other organisms, particularly the pyogenic cocci, are found associated with it, though not intimately. The membrane and necrotic tissue may also be invaded by fungi.

Membrane Formation.—This is due to a combination of processes. It seems probable that the first step in its production is degeneration and necrosis of the epithelium, often preceded by active proliferation of the nuclei of the cells by direct division. The cells may either break up into detritus, with fragmentation of the nuclei, or they may become changed into refractive hyaline masses. An inflammatory exudation rich in fibrin factors comes from the tissue below, and fibrin is formed when this comes in contact with the necrotic epithelium. The fibrin in part is formed into a reticulum around exudation cells and degenerated epithelium, in part it combines with the hyaline degenerated cells to form a hyaline membrane. The hyaline membrane is most often formed on those surfaces which are covered with epithelium having several layers of cells. It may be formed by a hyaline degeneration of exudation cells; in this case the spaces in the meshwork are smaller. It is probable that the fibrinous membrane is formed both on the surfaces and in the tissue. The fibrin is first formed around cells which afterward disappear. In the trachea the fibrinous membrane often has a definite structure. The membrane may disintegrate and be broken up into a mass of detritus (the process commences on the surface), or it may be cast off as a whole by being elevated by an exudation beneath. Very thick masses of membrane may be formed by the constant addition of fibrinous exudation. The membrane is never formed primarily on an intact epithelial surface, but it may extend over it. Nothing is to be gained by making an anatomical distinction between a croupous and a diphtheritic membrane. There is nothing specific in the membrane formation in diphtheria. We have found typical hyaline and fibrinous membranes in cysts of the ovary in the formation of which bacteria played no part.

The membrane formation is accompanied by changes in the tissue beneath, which represent a combination of degeneration and exudation. The connective tissue and blood-vessels undergo a hyaline, fibrinoid degeneration very similar to the degeneration of the epithelium. Necrosis may extend deeply into the tissue, but there is little tendency to deep ulceration or abscess formation. The degeneration in the mucous glands of the tissue is so pronounced as to be almost specific. Marked degeneration of the epithelium of the glands may be found without any change in the surrounding tissue. The changes in the blood-vessels, though so pronounced in diphtheria, are not specific. We have frequently found changes in all respects similar in the walls of abscesses and ulcers. The extent of the necrosis in the primary lesions is greater than is found in the action of any other bacteria.

Heart.—Degeneration of the myocardium is one of the most common conditions found in diphtheria. The simplest form of this is fatty degeneration, which is found in the majority of all cases. This varies in extent, at times affecting the myocardium generally, at other times occurring in foci. The fatty degeneration accompanies and seems to precede the more advanced forms of degeneration which lead to the complete destruction of the muscle. In this there is destruction of the sarcous elements, which become swollen, broken up, and converted into hyaline masses. Simple fatty degeneration is found in the severe cases of short duration, the more extensive degenerations in the more prolonged cases. The degenerations may be so extensive as to account fully for the impairment of the heart action. No bacteria are found in connection with the degeneration, but like most of the lesions of the disease it is due to the influences of the toxic substances in the blood.

Acute interstitial lesions of two sorts are found. In one there are focal collections of plasma and lymphoid cells in the tissue, which may be accompanied by degeneration of the myocardium, but are not dependent upon it. In the other condition the interstitial change consists of a proliferation of the cells of the tissue and is secondary to the degeneration of the muscle.

Thrombosis is not an uncommon condition and is due to primary necrosis of the endocardium. Lesions of the vessels of the heart play but little part; the only lesion of interest is proliferation of the intima, the same lesion which is frequently found in the vessels in other organs.

Lungs.—There is no organ in the body in which lesions accompanying diphtheritic infection are so generally found or so serious as in the lung. In very many cases they are so extensive that death may be regarded as due rather to the condition of the lungs than to the throat affection. We have frequently found extensive lesions on microscopical examination even when the lungs presented little or no change to the naked eye. It seems probable that the frequency of these lesions may be due to the fact that most or all of our cases were treated with antitoxin, and that those in which the lung complications were not present, or at least not severe, recovered.

The most common lesion is broncho-pneumonia. The term implies both the manner in which infection takes place and the relation of the foci to the bronchi. The process begins as an infection of the atria and from here extends. It may be limited to single acini, to lobules, or to groups of lobules. There is but little lateral extension of the infection through the walls of the alveoli or the bronchi into the surrounding air spaces. Acute inflammation of the larger bronchi usually accompanies the broncho-pneumonia, but is not constant. Atelectasis varying in extent from one to several lobules, or even confined to a few air spaces, is very commonly present. The same is true of emphysema. True acute lobar pneumonia was never found. The cases resembling this were found on closer examination to be cases of extensive confluent broncho-pneumonia. General œdema of the lung comparable to the circulatory œdema of adults was never found, although inflammatory œdema was common. The character of the exudation varies greatly. It may be fibrinous, hemorrhagic, serous, or almost entirely cellular. The cells in the exudation are partly leucocytes, partly cells derived from proliferation of the lining epithelium. Lymphoid and plasma cells also are found in the exudation. Cellular infiltration of the interstitial tissue and productive changes in it are common, both in connection with the acute exudative lesions and apart from them. In some cases organization of the exudation and the formation of connective tissue within the air spaces were found. Proliferation of the lining epithelium of the air spaces is frequent, and is always more pronounced in the vicinity of the pleura and the connective-tissue septa.

Thrombi are occasionally found in the larger vessels. Dilatation of the lymphatics is very common. They may contain coagulated albumen, fibrin, or cells. They are often found packed with lymphoid and plasma cells, and large cells similar to the large cells in the air spaces.

Nothing has shown so well how little the character of a pathological process is influenced by the character of the micro-organism as has the examination of these lungs. Pneumococci, streptococci, and diphtheria bacilli have been found in connection with serous, purulent, fibrinous, and hemorrhagic exudations, necrosis, and abscess forma-

* The section on Pathology is largely a summary of the recent and excellent monograph by Councilman, Mallory, and Pearce (Journal of the Boston Soc. of Med. Sciences, December, 1900).