Diphtheria is closely allied to scarlet fever, and it occurs during the course of measles, small-pox, typhus, puerperal fever, exudations developing in the fauces during the progress of these diseases, and on the genitalia in the last mentioned.* Indeed, it seems well established that the materies morbi of these low forms of fever favor the development of the diphtheria-poison. While the disease occurs more or less throughout the whole range of civilization, it is more prevalent in the temperate regions. It is more apt to prevail as an epidemic during the winter and spring, but epidemics have occurred at all seasons. Like all other diseases of the same kind, all the conditions of bad hygiene increase its virulence and favor its diffusion. Unquestionably, the chief cause of its spread is contagion. Many nurses and physicians have fallen victims to their devotion. "When it breaks out in a family, all the children are commonly affected with it, if the healthy are not kept apart from the sick; and such adults as are frequently with them, and receive their breath near at hand, seldom escape some degree of the same disease." † The experience of the last century is the same to-day. As a rule, the more severe the case of diphtheria, the more intense the activity of the poison. When there are several bad cases in a small apartment not ventilated, the poison becomes denser and more virulent, and conversely, when there is a single case in a large, well-ventilated apartment, the poison is diluted, and its virulence lessened. The young, above one year, are more susceptible than adults, the greatest mortality being attained from the second to the fifth year. Boys seem more apt to get the disease than girls, a fact which Fothergill noted in the epidemics of the middle of the last century. An acute catarrh of the fauces seems to invite the contagion, and although one attack does not confer an immunity against subsequent attacks, a considerable interval occurs between them. When we hear of children having diphtheria every year, we have a right to assume that errors of diagnosis have been committed. The poison of diphtheria exists in the exudations and secretions of the fauces, and it is chiefly by means of this that the disease is communicated. Those engaged in swabbing the throat receive this matter as it is ejected in coughing, or with the exhaled breath. Several physicians have been poisoned by blowing through a trachea canula. Articles of clothing may contain particles of matter for a long time adherent to them. Doubtless the poison floats in the atmosphere at a considerable distance from the original source. It adheres with considerable tenacity to the walls, floors, bedstead, and articles of furniture, but especially to bedding, carpets, curtains, and woolen goods of all kinds. Not all who come in contact with the germ or poison have diphtheria, for individual susceptibility

* Virchow's "Archiv," Bd. ix, s. 228, 1856.

† "An Account of the Putrid Sore Throat," by John Fothergill, M. D., fifth edition, London, 1769, p. 31.

and predisposition are important factors. When the predisposition exists, and exposure is effected, a certain interval elapses before there are any objective signs of the disease. This *period of incubation* is very variable, and the variations are due to the differences in the intensity of the poison and the systemic state of those poisoned. The more malignant the disease and the more depraved the bodily condition, the more quickly will the symptoms of the disease appear after reception of the disease-germs. If the poison come in contact with an abraded surface, it secures immediate admission to the blood, and then the stage of incubation may not exceed two days. Admitted to the system in the ordinary way, the period of incubation will vary from three to ten days. By Oertel it is placed at two to five days. According to the author's observations, the period of incubation during the epidemic prevalence of the disease is in the largest number of cases three days.

Pathological Anatomy.—Except for the nicer pathological distinctions of modern methods, we might adopt the description of Fothergill* as an account suitable for to-day of the lesions of diphtheria. The first change consists in hyperæmia—a vivid injection of the mucous membrane of the fauces. At the end of twenty-four hours a faint, grayish-white pellicle appears on the surface of the soft palate, the pillars of the fauces, the pendulum, or the tonsils. The patches may be no larger than pin-heads, and scarcely thick enough to prevent the membrane showing through them. In a few hours they greatly increase in number, coalesce over spaces having the area of three or four lines, and thicken, so that they appear like bits of curds on the surface of the membrane. Now there appear, constituting the exudation and piercing the mucous membrane, forcing apart the epithelial cells, great numbers of round bodies, highly refracting single cells with thick walls—the micrococci. Masses of them, united in bundles and colonies, form distinct nodules, projecting above and making their way into the deepest part of the mucous membrane.† Leucocytes—pus-corpuscles—soon appear, but not in great numbers, in the deep layers of the mucous membrane, and they are coated by micrococci, and these bodies have also penetrated their interior; but, as the process extends, pus-cells increase in number and spread out through the basement membrane and through the epithelial cells surrounding the micrococci colonies on all sides. Among the pus-corpuscles now appear young cells three or four times larger than the former, and they multiply in large numbers—their nuclei surrounded by a thin layer of protoplasm, accumulating also. Thus is formed a mass composed of micrococci, pus-cells, and newly formed cellular elements, which constitute a mem-

* Fothergill did not, as Bretonneau points out, properly distinguish the diphtheritic sore-throat of scarlet fever from diphtheria.

† Dr. L. Letzerich, "Beitrage zur Kenntniss der Diphtheritis," Virchow's "Archiv," Band xlvi und xlvii, 1869.

branous patch that may be lifted off the surface.* In the *croupous form* a quantity of fibrin is exuded when the local process has reached the development above described. This fibrin is poured out into the epithelium, and between the epithelium and the basement membrane or "sub-epithelial tissue." The epithelial cells rapidly undergo necrosis; a network of fibrin develops between them, and colonies of micrococci form in the outer layer of the false membrane. Succeeding exudations lift up the first-formed false membrane, and between them capillary hæmorrhages may take place, and thus the extravasated blood is inclosed in the meshes of the fibrinous exudation. Meanwhile the micrococci penetrate deeper, new deposits of fibrin occur, and hence the false membrane increases in all directions and new ones are formed. The membrane is detached and cast off by a cessation of the fibrin exudation and an abundant formation of pus elements. The micrococci penetrate to the lymphatics and lymph-canals, unless cut off from penetrating below by the abundance of the fibrinous exudation. The mucous membrane of the nose, larynx, and air-passages, undergoes similar changes in the process of formation of a false membrane. When recovery takes place the fibrin exudations cease, and the false membrane is broken up and detached by the abundant formation of merely purulent cells. The epithelium destroyed is restored by the formation of new cells produced from the sub-epithelial layer. In the *septic form* the masses of false membrane undergo decomposition, bacteria form in immense numbers, and the micrococci penetrate to the deepest part of the mucosa, filling in the sub-epithelial and sub-mucous tissues. It is generally conceded that the diphtheritic process as it occurs in the nose is more apt to produce septic infection. Here the micrococci accumulate in the greatest numbers, and seem possessed of the greatest activity; for the periosteum, the cartilages, even the bones, are attacked. *Gangrene* is produced in consequence of the rapid increase in cells, the exudations of fibrin, and the crowding of the tissues by micrococci, arresting the blood-supply and stopping the nutritive processes, hence causing a necrobiosis, which is extensive in proportion to the spread of the membrane formation. When this occurs, "false membrane mucosa, and submucosa form together one semi-liquid, discolored, dark pulp, or a darkish, wormwood-like, broken-down mass, or a dark, more firmly attached slough, from which the intense, peculiar odor of gangrene is spread." †

* Burdon-Sanderson long ago described, with his usual fidelity, the fibrin, the cellular elements, and the transparent granules (micrococci?) which unite to make up the false membrane. ("Contributions to the Pathology of Diphtheritic Sore Throat," etc., "British and Foreign Medico-Chirurgical Review," January, 1860, p. 179, *et seq.*)

‡ Jaffé, "Die Diphtherie," etc., Schmidt's "Jahrbücher," fünfter Artikel, vol. clviii, p. 73. Also, Oertel, *supra*.

The lymphatics of the neck, whose vessels take their origin in the tissues included in the diphtheritic process, are also involved. The micrococci penetrate to the vasa efferentia, and are seen crowding these vessels in large numbers. The lymphatic glands of the part—submaxillary, sublingual, parotid—and the chain of cervical lymphatics underlying the sterno-cleido-mastoid are enlarged more or less extensively. The periglandular and the general connective tissue are swollen, infiltrated with pus and lymphoid cells, and there may be also around the glands extravasations of blood. The swelling of the glands themselves is due to a hyperplasia of the cells, the stroma remaining unaffected. The membranous exudations, in a small proportion of cases, extends to the bronchi, but only involving a part of the tubes. The changes in the lungs are due to the mechanical obstruction of bronchi, the consequences being atelectasis, emphysema, and localized œdema. When the diphtheritic process invades the lung-tissue itself, there will be seen at various points extravasations of blood, and infarctions, and alveoli distended with cellular elements—epithelium, blood-corpuscles, and new cells, etc.—and micrococci colonies. In cases of septic infection, the muscular tissue of the heart becomes soft, is easily torn, and its fibrillæ are far advanced in fatty degeneration, while at various points are extravasations of blood into the muscular substance. Ulcerative endocarditis, due to the development of bacterian colonies, thickening and vegetations of the valves, with the secondary consequences of this condition of the endocardium, have been repeatedly demonstrated.* The composition of the blood is much altered in the cases of severe toxæmia: it is black, fluid, rather mucilaginous, and stains the fingers a brownish color. Important changes occur in the kidneys, and at a very early period of the disease. They are swollen, intensely hyperæmic in the severe cases, but little so in the mildest; but, in all cases, changes occur in the Malpighian tufts and in the tubules. The tufts are hæmorrhagic, contain micrococci colonies, and are surrounded by lymphoid cells; the epithelium of the tubules is cloudy, granular, and swollen, and is often detached in the form of casts with epithelium adherent. The brain is hyperæmic, and there are numerous capillary hæmorrhages, but the most interesting changes, which serve to explain the secondary paralyses, are those occurring in the spinal nerve-roots, which are thickened, while in the sheaths of the nerves hæmorrhagic extravasations occur, and they are also filled with lymphoid cells and nuclei. Important changes occur in the muscles, beginning at any point of infection. Capillary hæmorrhages † occur

* "Ueber diphtherische Endocarditis," von C. J. Eberth in Zurich, Virchow's "Archiv," Band lvii, s. 228, *et seq.*

† The constant appearance of capillary hæmorrhages, in various parts, referred to in the text, is regarded as highly characteristic. Jaffé, "Die Diphtherie," etc., Schmidt's "Jahrbücher," Band clvii, s. 73. An elaborate article, extending through five issues of the journal.

in them, and the striæ disappear in the course of a fatty and granular degeneration. Those muscles lying immediately under the affected mucous membrane are apt to undergo these changes, because invaded directly by the pathological products of the diphtheritic process.

Symptoms.—There are well-marked forms of diphtheria—the catarrhal, the croupous, the septicæmic, and the gangrenous. In the description of the morbid appearances these natural divisions were kept in view, and all who have had any considerable experience with the disease will recognize the adherence to nature of these phrases. In the *catarrhal form*, the initial symptoms are those of an ordinary catarrh. Heat, irritation, and pain are felt in the throat, and, on the attempt to swallow, much soreness is experienced. Chilliness followed by some slight fever, headache, backache, and general muscular pains are usually present, but in the mildest cases only some slight general *malaise* may result. In still other cases the symptoms may be more pronounced: high fever, severe sore throat, violent headache, *tinnitus*, considerable debility, nausea, and vomiting may be experienced. On examination of the fauces, there are seen more or less intense hyperæmia, and on the palate or tonsils minute grayish-white patches, very thin, and firmly adherent. The tongue is covered with a thick white coating, which extends well forward to the tip, and is also pertinaciously adherent to the organ. In a day or two, sometimes more rapidly, the patches of false membrane extend over the tonsils, the pillars, and the pharynx by a union of numerous centers of deposit, and not by a marginal growth only. The thickness of this membrane is at this time a line or two, and it is distinctly outlined against the dark-red mucous membrane about it. The color of the membrane is grayish-white, but it varies from that shade to dark red, or even black. The reddish tint is due to extravasation of blood, and inclosure of the blood in the meshes of the exuded fibrin. In the catarrhal form, however, but few cases attain to such an extent of false membrane; there are a few patches which may coalesce and be limited to one side, and they reach their maximum by the third day, when already the mucous membrane has become paler, and the exudation is loosening at the margins. The fever which appeared at the outset has by this time disappeared, but in most of the cases of the catarrhal form there is no fever, or it ceases after the first day. The general disturbance ceases with the fever, except the debility, which seems in marked contrast to the apparent severity of the disease. Soreness of the throat, pain in swallowing, and some tumefaction of the submaxillary and deep cervical glands continue up to the detachment of the false membrane, which may take place about the sixth day. When the false membrane is detached, the mucous membrane appears red and still swollen, but its continuity is restored by the production of new epithelium. In the more severe cases the detachment of the false membrane is not

effected until some days later, the debility is considerable, and convalescence requires several days longer. The mildest cases of the catarrhal form may be followed by diphtheritic paralyses and other sequelæ.

Croupous Form.—This form may begin as the ordinary catarrhal variety, and continues to the formation of the false membrane, without any indications of a departure from the usual course, until the fourth or fifth day, when it takes on a new character by the sudden development of a high fever, increased tumefaction of the glands, spreading of the false membrane, etc. When the case from the beginning assumes the severity belonging to the croupous form, it sets in with violent symptoms—with chilliness but not a chill, followed by high fever; or the fever begins at once with the onset of other symptoms, the temperature rising to 103°, 104°, or 105° Fahr. The usual symptoms of the feverish state are also present—headache, general pains, thirst, and restlessness at night, occasionally delirium. Then occur the special symptoms referable to the throat—a sense of heat and burning, and severe pain in the act of swallowing. The sublingual and submaxillary glands are swollen, and especially the deep cervical lymphatics lying under the sterno-cleido-mastoid, which are not enlarged in other affections of the throat. The swollen glands are hard and tender, and the infiltrated connective tissue about them is also sensitive to pressure. The mucous membrane is intensely hyperæmic in parts, especially on the pendulum, the palate, the pillars of the fauces, and the tonsils, and it is swollen and œdematous. On this dark-red ground appears, in a few hours, the false membrane in small patches of grayish-white, and, in the course of the next twenty-four hours it has developed into a thick, yellowish-gray membrane, which, becoming drier and darker, presents an appearance not unlike the rind of bacon. In the course of subsequent changes the false membrane assumes a yellowish-gray shade, somewhat like sole-leather. The change in tints is at first due to the inclosure of blood within the meshes of the exuded fibrin, and afterward to the great increase of the pus-corpuscles. If this thick, tenacious, leather-like false membrane is now removed, the epithelium comes with it, leaving a raw, dark-red, bleeding surface beneath. Another false membrane may form on this surface, or it may undergo healing in the mode already described. While the development of the local morbid process is proceeding, the general condition may improve, the fever declining to near normal, the appetite returning, and strength increasing. An arrest of the local process may be effected at the end of the first or beginning of the second week, the membrane become detached, and convalescence be slowly established. More frequently, however, while this apparent improvement is taking place, the false membrane is spreading in all directions. Usually, when no attempt at the arrest of the disease is made, the fever rises higher, the difficulty in swallowing

increases, and the patient is tormented by efforts to rid the throat of a tough secretion. At this period of the disease, a condition of profound adynamia may come on, and death ensue in collapse. Otherwise, the disease pursues its course, the false membrane extends, the swelling of the neck increases to formidable proportions, the salivary glands pour out a quantity of offensive saliva, and from the fauces is exhaled a horrible fetor which awakens suspicions of the setting in of gangrene. If the exudation does not extend to the larynx, the breathing, though heavy, is not dyspnœic, and the voice, though muffled and nasal, is not toneless. The appetite is utterly gone, the stomach rather unsettled, although vomiting is not usual, and the bowels are rather constipated, but vomiting and diarrhœa may both exist, caused, it may be, by the swallowing of the ichorous matters produced in the throat. The urine is scanty and high-colored, and in the great majority of cases contains albumen (Squire*), and the quantity of urea is increased —at the maximum of the disease, doubled. Casts of the tubules with epithelium, adherent and hyaline cases, have also been observed in the cases of albuminuria. When the disease has reached the point in its development just described, slow recovery may take place, as already mentioned, or the disease may extend into the nares, downward into the larynx and trachea, or into the Eustachian tube. As there are some special features introduced into the symptomatology by such extension of the morbid process, it becomes necessary to enter into brief details on these points. When the membrane spreads into the nose, a disagreeable sense of stuffing is produced, the patient breathes through the mouth, epistaxis frequently occurs, and an ichorous mucopurulent discharge flows from the anterior nares, excoriates the upper lip, and on this raw surface not unfrequently a false membrane forms. This is a serious complication, owing to the fact that septicæmia is very apt to be produced, and death may be caused by profuse epistaxis. The false membrane may spread up the lachrymal duct, and form on the conjunctiva, or, obstructing the flow of tears, cause epiphora. If the false membrane extends into the Eustachian tube, there will occur ear-ache, noises in the ears, deafness, etc. Extension downward into the larynx may take place early in the disease—from the third to the sixth day—or it may not occur until the end of the second week. Laryngeal diphtheria is more apt to occur in young children and in old persons (Oertel). The formation of false membrane may begin in and be limited to the larynx.† The capacity of the larynx being

* Reynolds's "System of Medicine," article "Diphtheria," vol. i, American edition, by Lea.

† "Relation of Membranous Croup and Diphtheria," "Medico-Chirurgical Transactions," vol. lii, p. 7. "The evidence before the committee is conclusive as to the fact that in epidemics of diphtheria cases do occur in which the false membrane is thus limited . . . . but such cases are exceptional."

greater in adults than it is in children, the symptoms of stenosis are more pronounced in the latter. Progressive difficulty of breathing, a hoarse, then toneless voice, the characteristic "croupy cough," are the symptoms of laryngeal diphtheria. These cases present the clinical history of croup throughout, and the reader is referred to the article on that topic for the details. These cases do not continue very long, and their termination is usually fatal, although recoveries do ensue.* They prove fatal by spasm of the glottis, by obstruction of the bronchi, by pneumonia, by carbonic-acid poisoning, etc. In the rare cases terminating in recovery, the false membrane is expelled by coughing, and no new membrane is produced. The fever and other symptoms subside with the improvement in the local condition.

Septic Form.—During the course of the catarrhal or croupous form, especially the latter, the products of decomposition entering the blood, the condition of septicæmia will be produced. The development of the systemic state is preceded by ichorous decomposition of the exudations and secretions of the fauces; a foul-smelling and very irritating fluid is discharged from the mouth; the lips are eroded by it, and on the erosions grayish-white patches of false membrane form. Numerous capillary hæmorrhages occur; the blood mixing with the decomposing membranes gives them a blackish appearance; and the whole mass, putrefying, presents a strong likeness to gangrene, but on removing the decomposing materials the mucous membrane beneath is seen to be merely hyperæmic, and capable of entire restoration. The glands of the neck and the neighboring connective tissue swell enormously, and present a shining appearance, and are hard or doughy to the touch. When the blood is poisoned, the constitution sympathizes profoundly. The face has a sallow, earthy, and pallid hue; the pulse is small, weak, compressible, and very slow; the temperature does not pass above 100°, and is more frequently at 98°, even lower; the appetite is gone, nausea, vomiting, and diarrhœa are usually present, the stools having a foul odor; the urine is small in quantity and loaded with albumen; and the strength is exhausted. Meanwhile the mental condition is that of apathy, the mind acting slowly but correctly, the intelligence becoming clouded only at the last. In other cases, the development of the septicæmia occurring more slowly, the phenomena are virtually the same—the main features being exhaustion, slow and irregular pulse (40 or 50 beats to the minute) or becoming rapid and thready, the temperature below normal (96° or 97° Fahr.), and weakness so great that fainting ensues on attempts to sit up, death usually occurring suddenly from failure of the heart. Recovery, it is claimed (Oertel), has been observed, but death is the

* "The mortality from this complication is alone very great; it has been estimated that one half of the fatal cases of diphtheria die from this accident" (Squire, *op. cit.*, p. 67).

usual result in a day or two after the development of the septicæmia, and very rarely later than four or five days after. When recovery is to take place, the pulse gains in volume, force, and frequency, the temperature rises, and the local condition improves. Convalescence is necessarily very slow.

Gangrenous Form.—This is an extension only of the septicæmic form, and should be so regarded. Gangrene attacks the infiltrated mucous membrane, and the exudations participate in the process. The affected parts turn black, and emit a horrible fetor. Before separation of the sloughs takes place, the blood is poisoned, and the patient rapidly passes into a condition of profound adynamia. Death is produced by thromboses, embolisms, failure of the heart, etc.

Course, Duration, and Termination.—The course and behavior of diphtheria have been sufficiently detailed in the preceding pages. The several forms described are based on sound observation and experience, which must always be confirmed. The mortality of diphtheria varies greatly in different epidemics, and the results of sporadic cases are influenced by numerous causes. In some epidemics nearly all have died. A mortality of one in three, one in seven, and one in ten, has been observed in various English epidemics. So great is the variety in the severity of epidemics and of individual cases, that no precise statement of mortality rates can be made. It is certainly true that no case of diphtheria should be regarded as trifling, for during the course of the simplest cases the most formidable symptoms may arise. The prognosis in any case is the graver, the more virulent the case from which the poison was obtained. The age and constitution of the individual attacked are of moment, for the mortality is much greater in young children, both on account of the danger of laryngeal implication and their feeble powers, and in those of any age who possess poor constitutions, are scrofulous, and enfeebled by bad habits and hygiene. The appearance of successive deposits, the occurrence of albuminuria, and the enlargement of the cervical lymphatics, indicate an extension of the disease. Extension to the larynx, as has already been pointed out, is in the highest degree unfavorable, and especially so in young subjects. Extension to the nasal passages is regarded as very unfavorable, both on account of the greater danger of septic infection and the interference with respiration. Jacobi, of New York, who is high authority, maintains that the unfavorable prognosis of nasal diphtheria heretofore made must be modified, if proper treatment is instituted. Much vomiting and purging are unfavorable symptoms, and in the same way must bleeding be regarded. If the specific gravity of the urine declines, and casts and blood-corpuscles are present, the temperature also rising, these symptoms are unfavorable. If the temperature should rise after the fifth day, it is suggestive of some new development, or of an extension of the exudation. A low temperature, below normal, a

cold and clammy skin, and a slow and irregular pulse, are of particularly evil import. Cases that are apparently doing well sometimes terminate very unexpectedly and suddenly by paralysis of the heart. As regards the different forms of diphtheria, the catarrhal is the most hopeful; next the croupous, and lastly the gangrenous. A majority of the catarrhal end in recovery—of the croupous in death.

Sequelæ.—Although the paralyses of diphtheria are really modes of manifestation of the poison, and are referable to changes occurring in nerve and muscle, it will be most convenient to study, together, those which occur during the existence of the other symptoms, and those which appear after the supposed termination of the disease. The latter group of paralyses come on two, three, even six weeks after the healing of the mucous membrane, but the former arise to complicate the case during the second week and subsequently. A nasal tone of voice, some difficulty in swallowing, and the regurgitation of liquids through the nose, are first observed. At length, complete inability to swallow occurs in the third or fourth week. On inspection, the palate is seen to hang limp and lifeless, and no movement is produced by irritation, the sensibility—as Trousseau long ago pointed out—being absent. The power of the heart is greatly reduced at the same period by extension of disease to the motor apparatus. The slowness of the pulse sometimes is phenomenal, the beats descending to 60, 50, 40, and in one case, reported by Sir William Jenner,* to 16 per minute. Paralysis of the heart may take place quite unexpectedly, and without any marked change in the ordinary conditions of the circulation. Paralysis of the respiratory muscles may also occur at this period, and may involve the phrenics and diaphragm, as in Sir William Gull's † case, or the intercostals and other chest-muscles. There is, probably, no difference, except as to rate of development and severity, between the cases of diphtheritic paralysis occurring in the second week and those which appear as sequelæ. The latter pursue a nearly definite course. They develop slowly but not until after healing of the mucous membrane, and begin in the muscles of the pharynx and soft palate, then involve the ocular muscles, and lastly the upper and lower extremities. These paralyses may follow the mildest as well as the more severe cases. The author saw a fatal case of diphtheritic paralysis of the muscles of respiration in a lady of sixty, who had been treated for a simple sore-throat two weeks before. Donders ‡ mentions the same fact: "Among the cases . . . . there were many in which the angina ran its course without important symptoms, several in which the angina was not recognized as diphtheria," etc. The

* "Diphtheria, its Symptoms and Treatment," p. 44.

† London "Lancet," vol. ii, 1858, p. 5.

‡ "On the Anomalies of Accommodation and Refraction of the Eye" (Sydenham Society edition, p. 607).