action ceased with the production of this injury. The tissue changes were the result rather of the injury produced by the agent than of the agent itself. It is possible in various ways to excite an inflammation in which all the phenomena which have been seen in acute inflammation develop much more slowly, or some of them may be entirely wanting, the whole process lasting much longer or even indefinitely. Such inflammations are termed chronic. It is of course impossible to assign any limits to the acute inflammations, and we cannot say that after so many days an inflammation ceases to be acute. The terms acute and chronic, therefore, while convenient, are difficult of definition. Chronic inflammations may be produced, first by the continuous action of an injurious agent, secondly by the repeated action of slight causes on a tissue which is not normal and not capable of resisting this action. In chronic inflammation, again, the changes in the tissue are marked and exceed in importance the exudation. The best types of chronic inflammation are seen in the inflammations around foreign bodies and in the ulcer. Inflammation surrounding foreign bodies may be studied by the introduction of various foreign bodies into the tissues of rabbits, and by the accidental material which is provided by surgery. Silk suture may remain in the tissues an indefinite time without undergoing absorption. The changes which take place are of two sorts: first, those which have for their object the absorption of the material (Plate XXXV., Figs. 1, 2); second, those which lead to the formation of an indefinite tissue which can resist the action of the foreign substance. Sections made across a silk suture which has been introduced into the muscles of the leg of a rabbit show in twenty-four hours around the suture an area of necrotic muscle. If the suture has been soaked in corrosive sublimate the fibres immediately adjoining it show no change. They have been killed by the corrosive and preserved in their normal state in the same way as muscle is hardened in a preservative. Such muscle fibres resist invasion by phagocytes. Farther out is an area where the nuclei of the fibres have disappeared and the fibres are swollen and hyaline. There is an abundant exudation of leucocytes which infiltrate the necrotic muscle and the suture. There is a slight new formation of cells in the surrounding tissue and the ordinary nuclear increase in the muscle nuclei. Sections made at late periods show first the degeneration and final disappearance of the leucocytes and the necrotic muscle fibres. The necrotic fibres are invaded by leucocytes, but it has not seemed to me that these are the true phagocytes. The final removal is effected by cells of the endothelial type (Plate XXXV., Figs. 1, 2) for which the way has been prepared by the leucocytes. The leucocytes all degenerate. The place of the exudation cells and necrotic tissue is taken by a tissue composed for the most part of spindle or irregularly shaped cells with large nuclei. Around the silk fibrils there are large protoplasmic masses containing a number of nuclei. These may surround the fibrils, and on longitudinal section are found to extend along them a considerable distance. These giant cells are formed from the cells of the tissue. They may be produced by coalescence of cells, or by the increase in size of a single cell with proliferation of nuclei but without succeeding division of protoplasm. They are formed about foreign bodies of all sorts. In wounds of the skin they are found with enclosed masses of connective tissue and elastic fibres. The silk fibres enclosed within them undergo no change even in the course of years. Sections made several weeks after introduction of the suture show that nearly all of the newly formed tissue has disappeared and the suture is surrounded by a thin mass of connective tissue, but which extends for some distance between the fibres of the surrounding muscle. The amount of the newly formed connective tissue varies greatly in different cases and according to the character of the material used for suture. It is very much greater around catgut than around silk suture. The catgut suture may remain unchanged in the tissue for a considerable time. It appears on section as a dense homogeneous mass surrounded by leucocytes, and later by newly formed tissue. Leucocytes do not invade it until cracks and fissures are formed in it. It appears rather to undergo slow softening and dissolution in the tissue than to be removed by phagocytes.

In the ulcer there is a combination of conditions. There is a constant trauma acting on the surface which has been deprived of its protective covering. The surface of a skin ulcer is always covered with a thin layer of necrotic tissue, within and below which there is an abundant infiltration with leucocytes. Extending to a variable depth below the surface there is a tissue composed of newly formed blood-vessels and of young connective tissue rich in cells. Between the cells of the connective tissue there are a few connective-tissue fibrillæ. The whole tissue is loose and œdematous, it contains great numbers of lymphoid and plasma cells, principally in groups around the vessels. The newly formed blood-vessels are large (Plate XXXV., Fig. 4), their walls are composed of large endothelial cells, with large nuclei, projecting into the lumen, and from them there is abundant emigration. This tissue remains until the surface is covered with a regenerating epithelium, and is finally replaced by dense connective tissue containing few cells or vessels. Such a tissue is made less resistant to traumatic influences than is normal tissue. In the first place it probably receives more injury from a blow or from pressure owing to its density and consequent inability to distribute the influences of the trauma. The blood-vessels in it are few in number and owing to the density of the tissue are less capable of quick dilatation and the increased nutrition necessary for repair. This condition is always to be considered in chronic inflammation. The repair of a tissue after an injury involving destruction of complicated structure is never perfect. Repair involving cells alone easily takes place and is perfect, but the tissues seem to have lost the power of forming again tissue of the same character as that produced in the embryonic condition. Chronic inflammation is frequently the result of repeated separate injuries produced by influences which come within the normal, acting on a tissue whose capacity for resistance and repair is low and which is continually lowered by each succeeding attack.

Healing of the abscess may take place in a number of ways. The exudation and with it most of the infectious agents which have been produced may be removed in the ways we have spoken of. There remains a surface which is very similar to the surface of an ulcer. It is infiltrated with leucocytes and contains numerous vessels and young tissue cells. The bacteria are partly removed, many of them are enclosed in phagocytic cells, the tissue has become resistant to the action of those that remain, and thus a local immunity is produced. The cavity becomes obliterated by the contraction of the tissue and the growing together of the walls.

It would be impossible within the limits of this article to consider further the special forms of inflammation due to the character of the tissue or the nature of the injurious agent. In certain organs the processes of inflammation may differ in a marked degree. In the kidney, for instance, there are lesions which come under the broad interpretation of inflammation which are not found in any other situation. In general, however, all the differences which are met with are but variations of the processes which have been described. *W. T. Councilman.*

INFLUENZA.—*Influenza* is an acute, self-limited, infectious fever, occurring in widely distributed epidemics, and characterized by catarrhal inflammation of the respiratory and gastro-intestinal mucosa, by profound nervous disturbances, and by extreme debility.

Synonyms: Febris catarrhalis; Epidemic catarrhal Fever; La Grippe; Grip; Tac; Horion; *La Dando; Ziep; Epidemischer Husten; Epidemischer Schnupfen; Schafhusten; Blitz-Catarrh; Modefieber; Mal Russe; Snufsjuka* (Swedish); *Qual-Tong* (Chinese).

Many other synonyms, grave and humorous, might be listed which have been suggested by the peculiarities of various epidemics, the national characteristics of the

people affected, or some fancied resemblance of the symptoms, but *influenza*, *la grippe*, or the Anglicized *grip*, have practically superseded all other names, in medical as well as lay circles.

Influenza is of Italian origin, and was probably first employed by the Italian savants to indicate the supposed occult influence of the stars over the course of the disease. Wolff states that it was first used by an Italian author, Gagliardi: "Parere sopra l'Influenza catarrale, che presentamente regna in Roma e stato ecclesiastico, Roma, 1733."

Other authorities, however, trace its origin to the English writers Pringle and Huxham, the latter of whom, in describing the epidemic of 1742–43, writes: "Quæ per totam Europam hoc vere sub nomine influenza grassata est."

The derivation of *la grippe* is likewise in doubt. Most authors refer its origin, and probably correctly, to the French, *agripper*, to seize, but others derive it from the Polish, *chrypka*, or *grypka*, hoarse. It came into general use in France during the epidemic of 1732 (Marigné: Description et traitement d'une affection catarrhale epidémique observée en 1732, vulgairement appellée la Grippe, 1776).

Historical Sketch.—Since the appearance of the fourth volume (1887) of this Reference Handbook, containing the brief article on *Influenza*, a series of epidemics has swept over the world, which, for rapidity of movement, extent of distribution, and numbers affected, rivals all previous visitations of the disease. This series, which began in the fall of 1889, was the first general epidemic of la grippe since 1847–48, and really introduced the present generation of practitioners to a disease known to them only in history, and thus became one of the notable medical events of the latter half of the nineteenth century.

Recurring at a time when the study of the infectious diseases was being pushed so zealously along bacteriological lines, and engaging in its study the ablest clinicians of every nation, it was confidently predicted that the mysterious problem of its nature and etiology would be speedily solved. While this prediction has not been thoroughly fulfilled, our knowledge of epidemic influenza has been materially increased and necessitates a restatement here.

In this necessarily brief historical sketch we shall not attempt a complete chronological account of the epidemics of all ages, but shall allude only to those which, from special incidents, mark an era in the progress of our knowledge, and endeavor to trace somewhat in detail the course of the recent epidemics of 1889–92.

Medical historians have interpreted the vague utterances of Hippocrates and Livy, referring to a disease which assumed epidemic proportions in 412 B.C., as the first written allusion to influenza.

Mention is made of an epidemic which prevailed extensively in the latter part of the sixth century, in which the prominent symptoms were headache, debility, cough, and an irresistible desire to yawn. Sneezing was usually the first symptom of the prevailing distemper, and the custom of calling down "God's blessing" upon one who was heard to sneeze is said to have originated at this time.

It is very probable, as maintained by many authors, that not a few of the general epidemics described in the earlier medical chronicles under various names (catarrhal fever, Italian fever, etc.) were epidemics of true influenza.

Parkes traces the disease back to the ninth century. In 827 and 876 epidemics in which cough was the most prominent symptom, and which also extended to domestic animals and birds, originated in Italy and spread rapidly over all Europe. The epidemic of 876 is said to have sadly discomfited the victorious army of Charlemagne on its return march from Italy.

But one epidemic, and that limited to Germany and France, is known to have occurred in the tenth century, after which the world apparently enjoyed immunity for about two hundred years.

Whatever may have been the nature of these early epidemics, our positive knowledge of influenza, according to Wilson, dates from the great visitation of 1510, which covered the whole of Europe and the British Islands, and was so general that "not a single family and scarce a person escaped it."

The epidemic of 1557, which appeared suddenly in Eastern Asia and spread rapidly to the West, was the first influenza epidemic which is known to have crossed the Atlantic to America. This pandemic was very severe in certain localities and was attended with a high mortality. Five thousand are said to have died in Delft alone within a short period.

During the past four hundred years there have been about seventy epidemics of grippe, one-half of which, from their widespread prevalence, deserve to be called pandemics.

The century just closed had thirteen visitations; the last important one previous to 1889 was that of 1847, in which were stricken more than one-quarter the population of London and Geneva, and fully one-half that of Paris.

The course of the later epidemics has been quite uniformly from east to west. It is, of course, only the general trend of the epidemic that can be followed, since every locality invaded becomes at once a new centre from which arms of infection reach out in every direction. With few exceptions, the later pandemics of influenza originated in Eastern Asia, where the disease may almost be said to be endemic. From this nidus they travelled westward across Russia, thence over continental Europe and the British Isles, over the ocean to America, Australia, East Indies, until, like Puck's girdle, they circled the globe.

The epidemic of 1889–90 followed closely the beaten path. The first cases of which we have knowledge occurred in Bokhara, Central Asia, in May, 1889. The disease became quite prevalent in July, and following the lines of the new railways slowly invaded other portions of the Russian empire.

The epidemic can be easily traced through Western Siberia and the post-towns and stations in Russia in its march toward St. Petersburg, which was reached by the end of October, and two weeks later it had assumed such startling proportions in that city as to attract the attention of the civilized world.

From St. Petersburg the epidemic spread with unprecedented rapidity, and the cities of Western Russia, Central and Northern Germany, Austria, France, and the British Islands became, in turn, the scene of its ravages, until by the end of December it had compassed the whole of Europe. Scattering cases announced the appearance of the disease in New York about the middle of December, and a week later it had assumed epidemic proportions. From the seaboard it extended in every direction, and during January, 1890, was generally diffused over the United States, British North America, the Sandwich Islands, and Central America (Guatemala).

From its starting-point in Central Asia the epidemic also extended in a southeasterly direction. Malta, Cyprus, and Egypt were successively visited in January and February. It was reported from India in February, became epidemic in March, and prevailed extensively in Upper and Lower Burmah during April and May. It reached Arabia in April, many of the pilgrims arriving from India and the Straits having sickened on the voyage.

In the Southern hemisphere the course was from the south northward. Cape Town was the seat of its first appearance in Africa, it having been carried thither by steamers; thence it extended northward, reaching Mauritius in August, the Shire Highlands in September, and Abyssinia in November, 1890.

South America was reached in February. Buenos Ayres was infected presumably by steamer from Bordeaux; thence it travelled up both coasts and prevailed in Brazil, Chili, and other states during April and May. It was notably severe in the province of Pernambuco. It

was prevalent in Australia and New Zealand from March to July.

In Iceland it occurred in July, and in some remote places of China and Kashmere during September and December.

Dr. Parsons, in his exhaustive report to the British Medical Association, July, 1891, to which we are largely indebted for the facts above related, writes: "Thus assuming the epidemic to have started from Russia in October, it took about six weeks or two months to spread over Europe and reach North America, rather more than two months to reach the Cape, three months to reach South America, four months to reach India, five months to reach New Zealand and Australia, nine months to reach Iceland, ten months to reach Mauritius, and nearly a year to make some remote places in Africa and Asia."

During the summer and fall of 1890 influenza was "smouldering on," as shown by the numerous local outbreaks, usually of short duration, in different parts of the world.

The second general epidemic—1891—began in January, and was but little less extensive, and probably more fatal, than the one just sketched. It, too, was pandemic, but in the journey around the world the course of its predecessor was reversed, and the general trend was from west to east.

The origin of the epidemic is traced to New Orleans, where influenza prevailed extensively and fatally in January, and from which it radiated in every direction. During February, March, and April it spread over the Northern States and was notably severe in Pittsburg and Chicago (March) and the seaboard (April). It was reported from England in April, from Germany in August, from Scandinavia and Denmark in July, from Russia (St. Petersburg) in September, from France in October, from Italy in December, and thus passed from country to country until almost the whole civilized world had been revisited. This epidemic also ran its course in about one year.

Since 1889 each winter has brought a recurrence of epidemic influenza, varying in extent and severity, to all parts of the world. Few American cities have escaped an annual visitation.

Nature and Etiology.—It has been customary to regard influenza as an epidemic catarrhal fever, but recent *dénouements* have materially strengthened the belief, long entertained by some, that it is really an infectious nervous fever.

Many of the symptoms are most readily explicable upon a neural basis, while its bacterial origin, together with the knowledge of the toxæmias that usually attend upon bacterial infection, gives support to such an explanation. Much testimony has accumulated during the recent epidemics to show that the nervous symptoms are primary and are followed by secondary involvement of the respiratory and digestive organs. In a given case the pulmonary, gastro-intestinal, or cerebro-spinal symptoms predominate as the nervous apparatus of one or the other system bears the brunt of the disease.

Nervous symptoms are uniformly present and usually pronounced, even in the mildest forms of grippe, while, on the other hand, in many of the worst cases, catarrh of the mucous membranes and inflammation of the respiratory tract are totally absent.

Again, when catarrh and pneumonia are present, they frequently assume "such a peculiar character as to lead to the suspicion that they might arise from irritation of, or loss of power in, the various nervous mechanisms supplying the affected parts, and would therefore have to be looked upon more as vaso-motor and trophic neuroses than as ordinary catarrh and inflammation."

The histories of the various epidemics prove clearly that the disease is not dependent upon climate, soil, season, meteorological or electrical conditions. It affects all classes of people, irrespective of nationality, sex, social position, or environment, although infants and young children seem to possess partial immunity. While no season of the year is exempt, late autumn and early winter are the periods of its greatest frequency.

The phenomena of influenza are comprehensible only upon the theory of a specific infecting virus or germ as the exciting cause. Its epidemic occurrence, transmission along lines of travel, rapid diffusion, sweeping over whole continents in a few weeks, and affecting nearly the entire population in a certain district in a few hours after its appearance, indicate some powerful morbific agent in the atmosphere which acts specifically upon the animal economy.

A few authors still cling to the theory that the morbific agent is a miasmatic material; but the generally accepted doctrine, and the one most in accord with our knowledge of the etiology of infectious diseases, is that which makes it dependent upon the presence of a microorganism.

For long the pathogenic bacillus eluded the vigilant search of bacteriologists, although from time to time its discovery was prematurely announced. Thus Weichselbaum's lancet-shaped diplococcus, Klebs' flagellatum, Jelly's hassock-shaped coccus, Kirchner's punctiform microbe, and Babes' radiated bacterium, each in turn failed in the crucial test and was relegated to obscurity along with Saulsbury's infusoria and Seifert's micrococci.

At the time of the last revision of this article (1893) Richard Pfeiffer had just announced the discovery of an organism which he regarded as the specific exciting agent of influenza.

This conclusion has been confirmed by later observers and is now universally accepted, although positive proof by the experimental reproduction of the typical disease has not yet been satisfactorily obtained.

Pfeiffer's bacillus is a tiny rodlet 0.8 to 1 μ long and 0.1 to 0.2 μ broad, about the same thickness and half the length of the bacillus of mouse septicæmia. It is the smallest bacillus yet isolated, and in cultures is recognizable during the first twenty-four hours only by means of a lens, so that macroscopically a test tube containing them can scarcely be distinguished from a sterile one. They are, however, readily differentiated by the peculiarity of their growth, as the colonies always remain separate and do not, like the colonies of other bacteria, join together and form continuous rows. When neighboring colonies come together the contours of the several colonies remain recognizable. Under the microscope they show a peculiar glassy transparency and are almost structureless.

The influenza bacilli are stained with difficulty. They respond either to a dilute Ziehl-Neelsen solution of carbol fuchsin or to a hot Löffler methylene-blue solution but do not react to Gram's stain.

The bacilli have been found in large numbers in sputum, bronchial, pleural and pneumonic exudations, and in the blood (Canon). They are present in such enormous numbers in the sputum of influenza patients that the bacteriological diagnosis is ordinarily a simple problem.

Inoculation experiments have been negative in most species of laboratory animals (mice, guinea-pigs, pigeons, etc.), but Cantani has recently succeeded in producing in rabbits a fatal form of influenza with profound nervous symptoms, by the intracerebral injection of living bacteria. And, contrary to the usual result of inoculations, the specific bacteria were found increased not only at the local seat of infection but also in the circulating blood and in remote organs.

It is highly probable that the action of the morbific principle of grippe is not limited to man. Epizoötics, very similar in many respects to the epidemics in the human race, have often prevailed among domesticated and wild animals, especially horses, dogs, and cats.

The attention of the profession was first called to this fact by Huxham in connection with the epidemics of 1732–33. These epizoötics occur independently, but more often happen either simultaneously with or immediately precede or follow epidemics of influenza. Bartholow favors the view that the epidemic disease in ani-