obtained from tetanic fluids, and that it would reproduce the symptoms of tetanus when injected into healthy animals. Rosenbach found the tetanus bacillus in human cases of the disease, and Nicolaier demonstrated its existence in soils. Kitasato soon afterwards obtained pure cultures of the bacillus, and demonstrated the immunizing power of the serum of animals inoculated with its toxin.

In laboratory experiments tetanus is prevented and cured by its antitoxin with almost absolute certainty, but the conditions are in every respect different from those which obtain in cases of accidental infection, the amount of toxin present in the animal being known, and the antitoxin being administered at the same time with the toxin or very soon afterwards. The disease is clinically unrecognizable until the nervous system has been sufficiently damaged to produce symptoms of nerve lesions, and the toxin is firmly united with the proteids of the central nervous tissue before symptoms develop, until which a diagnosis is impossible. The case is usually far advanced when professional assistance is first sought, and is therefore not so amenable to treatment as diseases which manifest their symptoms by progressive stages.

The study of tetanus statistics shows that its mortality prior to the use of antitoxin was from 70 to 90 per cent., in the acute form 80 to 90 per cent., and in the chronic type about 40 per cent. The available statistics of cases treated by antitoxin give the general mortality under this treatment as between 40 and 50 per cent., the reduction being chiefly manifested in the subacute and chronic cases, acute tetanus showing a mortality of 70 to 80 per cent. There is much difference between the results reported from certain countries, indicating a wide variance in either the potency of the sera employed or the virulence of the infecting bacilli. In Italy the disease seems to be amenable to antitoxin as well as to other methods of treatment, particularly that by phenol injections, while the reports from other countries are much less favorable.

On account of the natural difficulties in treating this disease by antitoxin at the late period when the symptoms are manifested, and from the fact that the serum is powerfully immunizing and harmless, the tendency is to adopt a prophylactic method in all cases, giving a full immunizing dose as soon as possible after the infliction of a wound received under circumstances which indicate a possible tetanus infection. For this purpose an injection of 10 Cc. of the serum will usually suffice, if repeated at intervals of a week or ten days. Along with this treatment the usual preventive measures should be employed, including excision of the part or the actual cautery if the wound is recent. The actual cautery, or the application of a strong solution of corrosive sublimate with tartaric acid, or the injection of phenol solutions, are the most effectual methods of combating the tetanus germs in the wound. For curative purposes the serum should be injected as soon as possible, the quantity being determined according to its stated strength, the gravity of the symptoms, the patient's age and the time since infection. The serum must be fresh to be effective, and the dose

is 10 to 20 Cc., repeated every 4 to 12 hours according to the severity of the symptoms.

Tetanus Antitoxin is manufactured in liquid form, also as a dry powder to be dissolved in a specified quantity of distilled water. One severe case, reported by Coffin, received 180 Cc. in seven days, with eventual recovery. The serum is usually administered subcutaneously, but is also injected into the brain tissue, and into the spinal subarachnoid space. Abbe trephined the skull of a boy 9 years old, and injected 3 Cc. on each side into the brain substance behind the fissure of Rolando two inches from the median line, giving 20 Cc. subcutaneously at the same time, the patient recovering. Letoux claims that the intracerebral injection is curative, while the subcutaneous one is protective, the latter affecting only that toxin which is on its way from the site of infection to the nerve centres.

Tuberculin, or *Koch's Lymph*, announced in 1890 as a remedy for tuberculosis by Professor R. Koch of Berlin, was subsequently stated by him to be an extract of the products of pure cultures of the tubercle bacillus, made with glycerin and water. In his preliminary statement to the International Medical Congress, the chief point made was that guinea-pigs could be rendered immune to inoculated tuberculosis by means of this agent, but even this has been denied by other observers. In his extended paper it was stated that the remedy would not directly kill the bacilli, but that it acted powerfully and specifically upon the living tuberculous tissue, caused a necrotic condition thereof and hastened its disintegration; also that it might be expected to increase the resistant power of healthy tissue and thereby starve the bacilli, check their increase, and lead in many cases to the cure of the disease. The actual result, however, as Virchow and others soon pointed out, was to soften and disintegrate quiescent deposits and to disseminate the bacilli throughout the body, forming new foci of active infection in other situations. The severe reactions, which followed the injections of the lymph in many instances, proved that serious risk must attend its general use; and that, like most remedies for phthisis, it could do good only in a few carefully selected cases.

Professor Koch acknowledged that tuberculin is only serviceable in the initial stage of phthisis and in cases of simple infection, also that when the case is complicated by the presence of other microbes it is of no service and often does harm. His statements as to its limitations were ignored in the enthusiasm excited by the discovery, the lymph was administered in advanced cases of mixed infection, and in poisonous doses, causing severe reactions, both local and general, so that many cases succumbed quickly under its use. A profound disappointment followed, tuberculin became thoroughly discredited, and its use was almost universally abandoned. It has become of interest again by reason of the efforts to extract from it a germicidal constituent free from toxins, also by the results obtained in tuberculosis with the blood serum of animals immunized by its repeated inoculation.

The violent action of tuberculin, together with its source, prove it to be a true bacterial toxin. Taken by the mouth it is inert, being probably digested in the stomach. In the dose of one milligramme injected hypodermically upon healthy subjects, it gives rise to slight pains in the limbs and a transient sense

of fatigue; but the same quantity injected upon tuberculous subjects produces a very powerful reaction both locally and generally, the constitutional effects being similar to those accompanying an acute exacerbation of the disease. About three hours after the injection a decided rigor occurs, which is followed by a rapid rise of temperature and pulse-rate; also pains in the limbs, a sense of great fatigue, drowsiness, nausea and loss of appetite, these effects lasting from 12 to 15 hours. In cases of advanced phthisis with cavities, after the injection of tuberculin the temperature has risen to 105.8° F., and this falling suddenly collapse has occurred and the patients have died. A local tuberculous lesion swells and becomes tender to the touch and the skin over it is inflamed. In pulmonary cases the reaction is greater than from the same dose in those having surgical tuberculous lesions; the cough increases, there are great distress and dyspnea, the patient feels decidedly worse and occasionally suffers a slight collapse. When the reaction has subsided the patient feels comparatively well and is generally better than before. In cases of lupus the effects of the injection are very marked. Within three hours there arises a feeling of tightness with heat and burning over the face and nose, and an eczematous exudation sets in, which continues about 48 hours and dries into crusts on the surface of the lesion. After two days these symptoms began to subside, and after nine days the crusts had fallen off and the affected tissue appeared shrunken, red and shiny, like the surface of a lupus patch which has been scraped with a Volkmann's spoon.

After tuberculin was discredited as a remedy, its composition became the subject of research, with the view of obtaining from it a remedial agent free from its toxic constituents. By chemical methods Klebs produced the derivatives *tuberculocidin* and *antiphthisin;* Von Ruck prepared a *purified tuberculin*, also an *aqueous extract* of the bodies of the bacilli; and Koch announced his *tuberculin-r* and the *new tuberculin*, which are emulsions of the pulverized bacilli, the latter being made with water and glycerin as a menstruum. These preparations have been extensively used during the last ten years, and have been the subject of a large quantity of literature from reputable physicians, many of whom are specialists in tuberculosis and its treatment. The present tendency is towards the recognition of Koch's new tuberculin and Von Ruck's aqueous extract, the preparations from the bodies of the bacilli, as valuable adjuncts in the treatment of this disease, if used in early cases of pure tuberculosis, and employed in connection with the recognized dietetic, climatic, hygienic, and medicinal measures.

Denison of Denver, after several years' experience with tuberculin and its derivatives, says that Von Ruck's aqueous extract is the most efficient among them, and reports 45 cases treated thereby, with 28 cases or 62 per cent. of cures. Von Ruck reports 303 watery extract cases, of which 56 per cent. were cured and 34 per cent. improved. Pottenger in 1902 made inquiry by letters addressed to 325 physicians, including many of the foremost European clinicians, and all known to be especially interested in the subject, and received 143 replies.

Of these 22½ per cent. recommended these preparations, 21 per cent. were hostile to them, and of 84 who expressed positive opinions on the subject 38 per cent. were favorable, while of all who acknowledged having had experience with these remedies 60 per cent. recommended them. Those favoring them based their opinions upon a total experience of 5,742 cases, those opposing upon experience in 813 cases. The same writer has collected statistics of 1,795 cases treated with various culture products, giving 45 per cent. of apparent cures, and 10,774 treated by other methods, with 14 per cent. of apparent cures. Of 589 first-stage cases of pure tuberculosis reported by Goetsch, Von Ruck, Jessen, Trudeau, and Rumbold, as treated with tuberculin or similar agents, 496 or 84 per cent. are stated to have been cured; while of 611 such cases treated by Bowditch, Clapp, Trudeau and Stubbert, without these remedies but in sanitoria, 391 or 64 per cent. were apparently cured. Goetsch alone reports 356 cases treated by tuberculin in small doses, beginning with $\frac{1}{10}$ mg. instead of 2 mg. as formerly, and states that 78 per cent. were clinically cured.

The therapeutic use of tuberculin is a toxin treatment, and when properly employed it benefits, either by stimulating the production of an antitoxin by the patient's tissue cells, or by the action of an immunizing or healing principle contained in it. It acts upon living tissue, and not upon the dead and decaying material existing in advanced cases; though in the latter it may benefit areas of recent extension which are purely tuberculous, and may produce immunity in unaffected tissue, thus preventing the further extension of the disease.

The use of tuberculin as a diagnostic agent is common with veterinarians, but has never been popular among physicians, they considering the ordinary methods to be sufficiently reliable for diagnosis. A subject is said to "react" to the tuberculin test, if he develops, within 12 hours after injection, a rise in temperature of 1½° to 2° F. or more, above the previous mean course of his temperature record. A rise of 1° F. or less is called a "mild reaction." Other symptoms may occur, as headache, malaise, and anorexia, sometimes vomiting and diarrhea. Three methods of making the test are in use,—(*a*) an initial dose of ½ to 1 mg., followed at intervals of 3 to 7 days by doses of 2, 4, and 10 mg. respectively: (*b*) an initial dose of 5 mg. followed by doses of 10 and 25 mg. at stated intervals; and (*c*) a single injection of 5 to 10 mg. By the latter method the mild or delayed reactions are avoided, also the possibility of establishing a tuberculin toleration, and the occurrence of cumulative effects.

Preparations (*Unofficial*).

Tuberculinum, *Tuberculin* (Koch),—is a glycerin extract of the culture fluid upon which the bacilli have been grown, concentrated to $\frac{1}{10}$th its original volume, and filtered through porcelaine to remove the bacilli. Initial dose, $\frac{1}{100}$ to $\frac{1}{10}$ mg., mixed with distilled water.

New Tuberculin, *Bacilli Emulsion* (Koch),—is a suspension of pulverized tubercle bacilli in glycerin and water, containing 5 mg. of the bacillar substance in each Cc. Initial dose, $\frac{1}{100}$ mg., diluted with normal salt solution.

Antiphthisin (Klebs),—is obtained by treating the original tuberculin with sodic iodide of bismuth, rejecting the precipitate, again precipitating with absolute alcohol, and dissolving this second precipitate in distilled water. Initial dose, $\frac{1}{10}$ Cc.

Tuberculinum Purificatum, *Purified Tuberculin* (Von Ruck),—is prepared by heating the culture fluid and the bacilli together *in vacuo* at a temperature of 130° F. for 2 or 3 months, and contains 1 per cent. of solid material. Initial dose, $\frac{1}{10}$ Cc.

Aqueous Extract of Tubercle Bacilli (Von Ruck),—is an extract prepared from the bodies of the bacilli freed from their fats, and contains 1 per cent. of solid material. Two additional solutions should be freshly prepared from this, one containing $\frac{1}{10}$ of 1 per cent., and the other $\frac{1}{100}$ of 1 per cent. of solid substance. Initial dose, $\frac{1}{10}$ Cc. of the weaker solution. When doses of 1 Cc. have been reached, this solution is abandoned for the next in strength, in order to avoid bulky injections. The dosage is gradually increased at longer intervals, up to a maximum of 1 Cc. of the original solution.

Tuberculosis Antitoxin superseded tuberculin for several years in the treatment of tuberculous disease, but does not seem to maintain its former reputation. Boinet immunized goats with injections of tuberculin, and used their serum in a few cases with decided benefit. Fisch injected horses with Koch's new tuberculin, and treated some 20 cases with their serum, reporting gratifying results. Paquin in 1897 reported on 393 cases, claiming 93 complete cures. Holmes in 1899 reported on 50 cases treated with most encouraging results. The reports of Ambler in 1899, and Stubbert in 1900, cover 136 cases, with 55 apparent cures. Mircoli in 1900 published statistics of 2889 cases, 385 of which were cured and 1064 improved. Maragliano of Genoa treated a large number of cases with serum obtained from immunized dogs, asses and horses. In 1899 he published statistics of 445 cases including his own and others, and stated that the local signs of the disease disappeared in 27 per cent. of the cases, the weight increased in 57 per cent., and the bacilli disappeared in 43 per cent. In 1901 he reported 130 cases treated by himself, of which 36 were cured and 58 improved. He states that cases of unmixed infection, with circumscribed foci of disease, slight surrounding consolidation, and but little fever, are distinctly benefited by the treatment and some are even cured thereby, but that those with much broncho-pneumonic consolidation or with cavities do not show any great improvement, and that it is impossible to cure without reinforcing the strength of the organism.

A study of the results obtained by the antitoxin treatment of tuberculosis shows that this serum is at best an adjunct to other measures; that if so used early in cases of unmixed infection it may bring about a cure, and when employed later in such cases it will retard the progress of the disease and promote healing; but that it is of no value in cases of mixed infection.

The dose depends on the particular serum employed; that of one manufactured in this country being stated at ♏iv–v daily, gradually increased to a maximum of ♏xv. Maragliano administers in apyretic cases or those with slight fever 1 Cc. of his serum every second day for the first ten days, then a similar dose every day for another ten days, then two similar injections daily for the next ten days. If there is high fever 10 Cc. should be given at once, and after three days a daily injection of 1 to 2 Cc. if the fever does not rise again, but if it persists a second dose of 10 Cc. is given eight days after the first one. Improvement is noticeable often within two weeks but sometimes not until after two months have elapsed. Even when a cure seems complete the injections should be continued for at least a month and even for a year. General hygienic measures must not be neglected, and the efficiency of the digestion must be especially attended to.

Streptococcus Toxin. The occasional disappearance of malignant tumors after an intercurrent attack of erysipelas suggested to Bruns and others the inoculation of cultures of the streptococcus erysipelatis as a remedial measure for inoperable cancer. The results, though favorable, were not so complete as in the cases acted upon by accidental erysipelas, and the inoculated disease often proved fatal to the patient. In 1894 Coley employed the toxin of the streptococcus instead of the culture itself, and reported a number of apparent cures. When it was found that the bacillus prodigiosus intensifies the virulence of the streptococcus, he used the mixed toxins of both germs, and later employed

their unfiltered toxins containing the dead bacteria, with better results than those obtained with the streptococcus toxin alone. The effects upon carcinoma were found to be slight, but were very marked upon sarcoma, especially the spindle-celled form. This treatment is employed only in cases which are manifestly unfit for operative interference. Virulent cultures of the streptococcus pyogenes are grown in the incubator for three weeks, then inoculated with the bacillus prodigiosus, and allowed to grow for ten days longer, when they are sterilized at a temperature of 140° F., and are then ready for use. The initial dose is ♏½, diluted with normal salt solution or sterilized water, injected hypodermically in the vicinity of the tumor or into the tumor itself. The size of the dose is gradually increased, and the injections are administered daily over a period of several months' duration. In one case they were given for 3 years, with occasional intervals of rest. When care is taken to secure asepsis, and to avoid excessive dosage, the treatment is said to be practically without danger.

In 1898 Coley reported that one-half of the spindle-celled sarcomata thus treated had disappeared; and in 1900, after experience in 230 cases, he reaffirmed his previous conclusions. In 1901 he reported 16 cases of inoperable sarcoma successfully treated by this method, and remaining well for periods varying from 3 to 8½ years. In 1902 Winberg reported a desperate case of round-celled sarcoma of the upper jaw with metastases, which was cured in five months by daily injections of Coley's toxins administered by injection into the abdominal wall. On the other hand, Senn states that in all his cases this treatment failed to effect even temporary improvement, and Wood has seen the added burden of septicemia thereby induced, and proving disastrous to a system already exhausted by cancer.

Antistreptococcus Serum has been employed successfully in erysipelas, puerperal fever, and several forms of septicemia and pyemia due to streptococcus infection. Marmorek, who originated this treatment, maintains that all streptococci produce the same toxin, and that the serum of animals immunized against one form of streptococcus is effective against the toxins of all varieties. Other observers generally disagree with him in regard to these contentions, and are endeavoring to produce a serum which will be as polyvalent as possible, by immunizing with many species of streptococci. It is generally conceded that this serum is harmless, and that in cases of pure streptococcus infection it will destroy the organisms and control the symptoms caused by their toxin, unless used too late for any remedy to be effective. Some authorities consider it neither bactericidal nor antitoxic in its action.

Marmorek treated 411 cases of erysipelas with his serum, and reported a mortality of only 3½ per cent. He used it also in 16 cases of puerperal fever, of which seven, due to streptococcus infection, recovered; one, due to bacterium coli, died; and among eight of mixed infection with streptococcus, bacterium coli and staphylococcus, five died. Williams reported 14 cases of severe puerperal septicemia treated with this serum, and 2 deaths. Reports of 70 cases so treated by various physicians show only 2 deaths; among them being 29 of erysipelas, 15 of puerperal septicemia, 11 of infected wounds, and smaller numbers of septic cellulitis, cerebro-spinal meningitis, scarlet fever, septic measles, pyemia, and acute gangrene. Packard and Wilson found records of

117 cases treated with antistreptococcus serum during 1901–2, of which 114 showed either a marked temporary improvement or a prompt recovery. These cases included puerperal septicemia, erysipelas, tuberculosis with pyogenic infection, general pyemia, local streptococcus infections, and a few cases of simple and pernicious anemia which seemed to be decidedly improved by injections of this serum. A combination serum, obtained from animals immunized by injections of both diphtheria toxins and streptococcus cultures, is used in advanced cases of diphtheria with double infection.

Antistreptococcus Serum is obtained from the horse immunized by inoculations with cultures rendered highly virulent by passing them through several rabbits, and then grown on a medium which preserves their virulence. After injection for a year with such cultures of the living streptococci of gradually increasing toxicity, the animal's serum is considered sufficiently powerful for use. There is no recognized unit of strength, therefore no general dose can be stated, but the manufacturer's directions in this respect may be followed.

Antipneumococcus Serum has given satisfaction to some physicians in the treatment of pneumonia. The reports of De Renzi, Fanoni, Eichberg, and Wiesbecker, covering 73 cases, give a mortality under the serum treatment of 6.8 per cent. On the other hand, J. C. Wilson has collected 162 cases from all sources, with a mortality of 16.6 per cent., and reports 35 cases so treated by himself, with 10 deaths, a mortality of over 28 per cent.; while at the same time of 20 cases treated without serum only 4 died, a mortality of 20 per cent. A later report by the same writer, based upon 36 cases, concludes with the statement that the results of this treatment do not encourage its continuance in croupous pneumonia. Other observers report disappointment as to the curative effects of the serum, but generally find that it improves the bodily comfort of the patient, and relieves many of the symptoms. Eichberg states that in 5 cases which recovered its administration was followed by almost complete cessation of cough and expectoration, and that the subsequent resolution was apparently accomplished without liquefaction. Rochester treated a case with a serum obtained by blistering another pneumonic patient, and observed marked benefit therefrom. Elfstrom took blood from patients suffering with pneumonia by leeching their arms, diluted it with normal salt solution, sterilized it by heating to 140° F. for two hours, and treated several patients with injections of this preparation, obtaining thereby a more rapid convalescence in the majority than is usual in this disease.

This serum has so far been of low and varying potency, due to the difficulty of obtaining sufficiently virulent cultures of pneumococci, but it is believed that when more active sera are obtained the results will be more favorable. The usual dose is 20 Cc. hypodermically every 4 to 6 hours, while the temperature exceeds 103° F.

Typhoid Sera, both the toxic and the bactericidal forms, have been used for several years, but the results have not been very encouraging. Inoculations with sterilized cultures of the bacillus typhosus were employed as a preventive measure in the British Army in India and South Africa, and in 1902 Lord Stanley announced in parliament that a report had been received, dealing with 4,138

cases, and showing a mortality of 8.2 per cent. in the inoculated, against 15.1 per cent. in the uninoculated. It is generally acknowledged that the preventive serum produces only a partial and temporary immunity, but that under its influence the disease pursues a milder and less fatal course than is usual.

In the opinion of those who have studied the question, a curative serum for typhoid fever should be both antitoxic and bactericidal, and also polyvalent by the use of toxins from many species of the bacillus typhosus. Chantemesse cultivates the bacilli on a filtrate of emulsion of splenic tissue digested with pepsin, carefully excluding the air, and with the toxin so obtained inoculates horses for more than a year. Of 100 cases of typhoid fever treated with his serum, he reports that all recovered in whom treatment was commenced before the tenth day of the disease, also all the others except six. In 1903 he compared 186 cases treated at his hospital by serum, cold baths, and other means, in which the mortality was only 3.7 per cent., with 1,478 cases treated at the same time in 15 other Paris hospitals, in which the mortality was 19.3 per cent. He administers an initial dose of 10 to 12 Cc. to vigorous adults, but a smaller dose, 6 to 8 Cc. if the treatment is commenced on or before the fifth day of the disease. If after a week the temperature remains high, he gives another injection of 4 to 10 Cc., according to the height of the fever.

Jez of Vienna has reported a number of cases treated by him with an extract from the spleen, thymus, marrow, brain, and spinal cord, of rabbits immunized against the typhoid bacillus. Eichorst reports 12 cases treated with this extract, all of which were of severe type, and all recovered.

Cholera Sera have been employed in epidemics of Asiatic cholera with considerable success. Tetrop, who studied the epidemics of 1892–94, claims that the benefit of serum was markedly evident in cases in which it was the only treatment employed. During an epidemic at Nagasaki in 1902 the Japanese physicians used a protective toxin inoculation and an anticholera serum, prepared in the imperial laboratory at Tokio under the direction of Dr. Kitasato. All persons employed at the quarantine station and in the cholera hospital received two immunizing injections, and although constantly in contact with the disease no case of cholera occurred among them. In some 700 cases of cholera the mortality was only about 35 per cent., but very few cases proved fatal when the serum treatment was administered within reasonable time. These statements were made by the Japanese medical officer in charge of the quarantine hospital to American army surgeons who were stationed there in attendance on their own cholera patients removed from a transport in September, 1902. The epidemic of that year in the Philippine Islands had a mortality of fully 75 per cent. with the ordinary treatment carried out under American medical supervision.

The studies of Lazarus and Pfeiffer showed that the blood-serum of persons who have recovered from Asiatic cholera is protective to animals against fatal doses of the cholera spirilla, and that this property is bactericidal rather than antitoxic in character; also that the dead spirilla are themselves toxic, and capable of acting similarly to the living germs. Haffkine cultivates the spirilla in bouillon

and then kills them by the application of heat, without destroying the toxic material which adheres to their bodies. The inoculation of human subjects with this product is followed by severe reaction, both local and general, and is believed to cause the production of a protective principle in the blood-serum. A preliminary inoculation is made with a weak virus, which produces a mild reaction, and after five or six days a more virulent preparation is injected, the reaction subsiding in another five days, when the subject is believed to be protected. In 42,445 such inoculations no mishap or injury to health resulted, and the British medical officers who were assigned to the duty of verifying the effects report that these were highly favorable, and that the statistics demonstrate for this method a remarkably protective power against Asiatic cholera in a country where the disease is endemic.

Plague Sera have been extensively used in recent epidemics of that disease, and although the commissions sent to India from England, Germany and Russia reported unfavorably upon the results obtained by them, the experience of individual observers indicates a decided, though as yet indefinite value for the serum-therapy of bubonic plague. The curative sera seem to have but slight influence on the mortality-rate in virulent epidemics, but in mild ones they exert a marked beneficial influence. The preventive inoculations have been more successful, and in some localities have practically eradicated the disease. Haffkine's protective serum is a toxin preparation, obtained by the same method as his cholera serum, and employed by a similar manner of administration, two injections being given about six days apart. It causes local and general reactions, which are more severe after the first inoculation. Yersin's curative serum is both antitoxic and bactericidal, and is obtained from horses immunized by injections of plague bacilli. After its use Calmette found that phagocytosis began at once, and the bacteria disappeared within a few hours. The temperature dropped in 4 to 5 hours, but often rose again for 8 to 12 hours, and finally fell at the beginning of an early convalescence. Lustig's serum is obtained from animals immunized with a nucleo-proteid extracted from dead plague bacilli by treatment with acids and alkalies. The use of Haffkine's serum in India is said to have reduced the number of cases to $\frac{1}{20}$ the number occurring in the uninoculated. Pinto reports from Brazil that only one person contracted the disease out of 1803 inoculated, and that in a certain district the only case of plague occurred in a man who had refused inoculation. Statistics of 2209 cases treated by various physicians with curative sera show a mortality varying between 13 and 59 per cent., against 80 per cent. and more in those treated by other methods. Lustig and Galeotti state that in an epidemic in India in which the general mortality was about 94 per cent., the mortality under the serum treatment was about 47 per cent.

The dose of the curative sera is large. Calmette gave 20 Cc. of Yersin's serum intravenously, and repeated the injections daily, sometimes giving 320 Cc. in one day. Choksey recommends doses of 60 to 100 Cc. of Lustig's serum, up to 300 Cc. or more, administered hypodermically.

Rabies Toxin. There is abundant proof that the specific virus of rabies is produced by a micro-organism, though none such has yet been demonstrated by the bacteriologists. Pasteur discovered that the virus is most abundant in the spinal cord of the rabid animal and showed that its inoculation upon a healthy animal will produce the characteristic symptoms of the disease, also that the virus may be attenuated in virulence by drying the spinal cord containing it. He also found that by the repeated inoculation of viruses of increasing virulence an animal is rendered immune to rabies, whether the infection is introduced by the bite of a rabid animal or by any other method of inoculation. Upon these facts he founded his preventive treatment of this disease, which consists in the daily inoculation of the bitten person with emulsions of gradually increasing virulence, made from the dried spinal cords of rabbits that have died from inoculated rabies. By this procedure chemical substances (toxins), produced during the life of some specific organism and known to be inhibitory of its growth, are introduced into the system of the patient (V. Horsley). The period of treatment is usually 15 days, during which from 2 to 6 inoculations are administered daily with viruses of gradually increasing intensity; the number depending on the time which has elapsed between the infliction of the bite and the commencement of the treatment. This method received the unqualified endorsement of a special committee appointed by the parliament of Great Britain in 1887, the members of which included the most eminent surgeons and physicians of England.

Statistics published by the New York Pasteur Institute state that from 1897 to 1901 inclusive 658 cases were treated at that institution, with a mortality of 0.76 per cent.; and at the Paris Institute during the same period there were 7,341 cases treated, with a mortality of 0.3 per cent. The two sets together give 7,999 cases treated, with a mortality of 0.34 per cent.

Rabies Antitoxin. Tizzoni and Cantani have published reports on the cure of rabies after its actual outbreak. They found that an alcoholic precipitate from the serum of highly immunized animals not only gave protection against rabies, but also cured the disease even after its first symptoms had manifested themselves.

Antisyphilis Serum.—The blood-serum of lambs and dogs was used by Tommasoli and other Italian experimenters in the secondary and tertiary manifestations of syphilis, with encouraging results. It was then suggested that the natural insusceptibility shown by certain animals to this disease might be increased by injecting into them the blood serum of human subjects in the primary or active secondary stages of syphilis. This has been carried out by Triboulet and others, without prejudicial effect on the animals injected, and their serum was used in the treatment of extensive tertiary ulcerations, with the result that these lesions almost completely disappeared, although they had resisted a six months' course of the ordinary treatment. Hericourt records a striking improvement in a case of syphilitic tabes under the same method, and other similar observations have been reported with equally favorable results. The doses employed were 2 Cc. of the serum on successive or alternate days.

The only complications observed were a transitory roseolar eruption, slight albuminuria, and a brief elevation of temperature. Moore has used the serum of syphilitics as a remedy for the disease in 75 cases. He obtains it by blistering syphilitic subjects, injects 10 to 40 Cc. every third day, and reports that it never failed to arrest the symptoms. Used locally upon chancroid it had no effect, but on chancre it produced a marked change in a day or two, with cicatrization in a week, thus acting as a valuable differential measure between the two lesions.

Antivenene. The active principle of serpent venom is a toxalbumin, analogous in character to the bacterial toxins. When taken by the mouth it is harmless, but is then antidotal to itself administered hypodermically or intravenously. By forced filtration it may be divided into two principles, one of which is toxic, but is digested in the stomach; the other is antidotal to the former, and passes from the stomach into the blood. Venomous serpents are almost immune to serpent venom, non-venomous ones share this immunity in a less degree, and the mongoose and some other animals possess it in marked degree, probably by inheritance from many generations of bitten ancestors. Sewall in 1887 showed that pigeons can be immunized against crotalus venom by successive and increasing inoculations of the poison. Calmette discovered that the blood-serum of an animal so immunized is protective against the effects of the bite of a venomous serpent, and Fraser found that when immunization is performed with cobra venom the resulting serum is protective against the virus of several other serpent species.

Calmette's is the recognized serum remedy for serpent bites, and has been used successfully in many cases. While particularly effective against cobra venom it is less efficient against that of the crotalus and other vipers, though of decided value in all forms. Its action is said to be directed to the nervous effects of the venom, rather than to its irritative and tissue-destroying qualities. It has been employed in cases of undoubted leprosy with excellent results, having brought about cures after other treatment had completely failed. The dose is 20 to 40 Cc. repeated frequently, but other recognized measures should not be neglected. A ligature should be applied above the wound, which should be laid open, well sucked, and surrounded by injections of an aqueous solution of calcium chloride.

The liver of venomous serpents is used by African witches in the preparation of a cure for snake-bite, and the Tarahumare cliff-dwellers of Mexico use for the same purpose the bile of the biter serpent locally to the wound, at the same time eating the serpent's liver as a remedy. Fraser states that the bile of a venomous serpent is an effective antidote to its poison. Calmette affirms that tetanus antitoxin antagonizes the effects of cobra venom to a certain extent, and that intravenous injections of calcium hypochlorite produce a serum which is antitoxic to the cobra poison.

Mallein is a glycerin extract of the culture products of the bacillus mallei, the micro-organism of glanders. When this toxin is injected into animals affected with that disease, it produces a strongly marked febrile reaction, similar to that caused by tuberculin in tuberculous subjects. It is extensively employed in veterinary practice for the purpose of testing horses suspected of being infected

with glanders. An antitoxic serum, obtained in the usual manner, has been used in a few cases of human glanders; one of which, reported by Dupuy, recovered under its administration from a severe attack of the disease.

Other Sera. Shiga prepared an *Antidysenteric Serum* which was used in 266 cases with a mortality of 8 to 12 per cent., while 1676 cases treated otherwise at the same time gave a mortality of 28 to 40 per cent. Rosenthal used a serum obtained from immunized dogs, which was bactericidal as well as antitoxic, and was used in 157 cases with a mortality of 4½ per cent. *Anti-anthrax Serum* was employed in 130 cases reported by Dasso, with a mortality of less than 7 per cent., also in 3 other cases without a death. *Antilepra Serum* has been used in a few cases with good results; and a toxin named *Leprolin*, obtained from lepra bacilli cultivated in a special medium, has been employed by Ross of Calcutta on lepers, with marked improvement in the condition of the patients, some cases showing almost complete subsidence of the disease. *Yellow Fever* has been treated with a serum obtained from dogs and rabbits immunized against the bacillus icteroides, with unimportant results, but Agramonte used the blood-serum from convalescent patients in 5 cases, 4 of which recovered promptly. *Scarlet Fever* has been treated with blood-serum from scarlatinal patients, with the result of shortening the course of the disease and causing marked amelioration of the symptoms. *Pertussis* was treated by Sylvestri with blood from the arm of a pertussis patient, mixed with an equal amount of saline solution, then shaken with chloroform and filtered. This preparation was injected into 5 children suffering from the disease, with the effect of improving the symptoms promptly, the cough and broncho-pneumonia disappearing in 8 to 11 days. In *Erysipelas* Jez employed the serum obtained by blistering a subject of the disease in 10 cases, with rapid improvement in all. *Vaccinia Antitoxin* is supposed to exist in the blood of vaccinated heifers, and Béclère has treated a few cases of variola with such a serum, in one case using 1,560 Cc., the patient recovering rapidly without suffering any serious inconvenience. In another case, an infant 21 days old with severe small-pox, the serum was injected to the amount of $\frac{1}{20}$th of the child's weight, with curative result. *Hay Fever* has been the subject of experiment by Dunbar, who isolated from the pollen of certain grasses a toxin, which applied to the eyes and nostrils of susceptible persons produced the characteristic symptoms of the disease. By injecting the pollen into animals he produced a serum, which quelled the symptoms of hay fever in subjects on whom they were induced. *Thyroid Serum* or *Antithyroidin* is obtained by Mœbius from animals whose thyroid glands had been extirpated six weeks previous to the bleeding. The preparation supplied by Merck is taken from thyrodectomized rams, and contains ½ per cent. of phenol. It is used internally (not hypodermically) in doses of 10 minims, gradually increased to a maximum of 80 minims, thrice daily; and has given satisfaction in exophthalmic goitre. *Morphine Antitoxin* is a serum taken from animals immunized by the injection of morphine for 3 to 5 months. It has proved preventive