



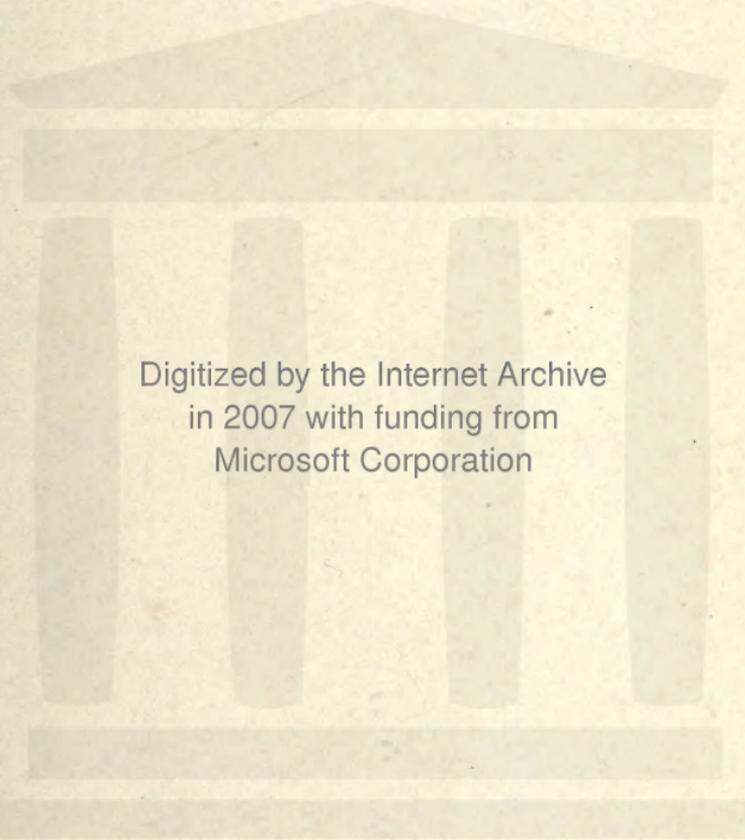
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# MODERN BIOLOGIC THERAPEUSIS

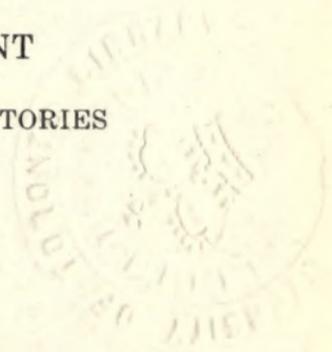
A CONCISE AND PRACTICAL TREATISE  
ON BIOLOGIC PRODUCTS FOR THE  
USE OF PRACTITIONERS IN THE  
MODERN APPLICATION  
OF IMMUNOLOGY TO  
THERAPEUTICS

ILLUSTRATED



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## PREFACE



## Preface

The object of this book is to furnish the busy practitioner with an outline of the historic development of medicine; to give him many important facts which may be of use in his professional work or which may be desirable for him to know as a part of his medical education; and to provide him with a handy reference compendium on vaccine and serum therapy.

In submitting this work to the medical profession, our aim has been to state concisely and accurately the present understanding concerning the clinical application and value of immunology; and to present the subject in such a manner as to be of the most assistance to the practitioner.

The scope of this little volume is not intended to embrace a complete description of all biologic preparations used in the practice of medicine; but only such products as are prepared by our laboratories have been discussed. An enormous literature pertaining to biologics has accumu-

lated, but no attempt has been made to record herein all the literature references on the subject; only a few of the more recent and important references being cited.

We are indebted to Dr. William H. Park, Director of the Bureau of Laboratories of the New York City Department of Health, for the privilege of using his copyrighted illustrations of bacteria. Some of the photographs of the pioneers in immunology are from portraits in Library Hall of the Army Medical Museum at Washington, D. C.

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# MODERN BIOLOGIC THERAPEUSIS

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## Part I HISTORIC DEVELOPMENT OF IMMUNOLOGY

### Chapter I HISTORY OF MEDICINE

#### PRIMITIVE MEDICINE

The common point of convergence of all medical folklore is the notion that spirits are the cause of disease. Primitive medicine is inseparable from primitive modes of religious beliefs. Disease at first was regarded by savage man as an evil spirit to be cajoled by burnt offerings and sacrifice. A further association of ideas led him to regard disease as something produced by a human enemy possessing supernatural powers. Again, what he saw in dreams suggested the existence of a spirit world apart from his daily life, and in this way he came to look

upon disease as the work of offended spirits of the dead. These three views of disease are common beliefs of the lowest grades of human life. Savages as a rule cheerfully accept all three, while a lingering belief in human sorcery and the displeasure of the dead is always a trait of the peasant.

For instance; almost any one who is living in the country will be familiar with various rural superstitions relating to warts—that killing or handling a toad may cause them, and that they can be removed by some one touching them with pebbles; or, with the notion that stump-water is good for freckles, while bad eyesight can be remedied by the water in which the blacksmith has dipped his red-hot iron. As a remedy for whooping-cough in Norfolk, England, a spider was tied up in a piece of muslin and pinned over the mantel piece; in Suffolk, to dip a child head downward in a hole dug in a meadow; in Yorkshire, owl broth; in other parts of England, riding a child on a bear. It was White of Selborne who described the most recent form of this folk-belief, which consists in passing a child afflicted with hernia through a cleft in an ash-tree. As late as 1895, such trees were described as exist-

ing for this purpose in Suffolk and Richmond Park, and there was once a similar tree in Burlington County, New Jersey.

*Color* is a factor of great moment in folk-healing; red, in particular, which the Chinese and New Zealanders regard as hateful to evil spirits, and other peoples as a heat-producer. Red silken bands, necklaces of coral beads, red pills and red fire, as well as the red coral ring and bells with which the baby cuts its teeth—all have had their superstitious associations; and the virtues of the familiar red flannel cloth worn about the neck for sore throat and whooping-cough were supposed to reside not in the flannel but in the red color. Finsen's red-light treatment to prevent pitting in smallpox was once an ancient folk-belief known to the Japanese.

The history of the advancement of medical science, however, is the history of the discovery of a number of important fundamental principles leading to new views of disease, to the invention of new instruments, procedures, and devices, and to the formulation of public hygienic laws—all converging to the great ideal of preventive medicine; and this was accomplished by

the arduous labor of a few devoted workers in science.

### GREEK MEDICINE

European medicine begins properly in the Age of Pericles and its scientific advancement centers in the figure of Hippocrates (460-370 B.C.) who gave to Greek medicine its scientific spirit and its ethical ideals. The eminence of Hippocrates is three-fold: he disassociated medicine from theurgy and philosophy; crystallized the loose knowledge into systematic science, and gave physicians the highest moral inspiration they had. Instead of attributing disease to the gods or their fantastic imaginations, Hippocrates virtually founded the bedside method which was afterwards employed with such signal ability by Sydenham, Laennec, Bright, Addison, Duchanne and Charrot.

It is the method of Hippocrates, the use of the mind and senses as diagnostic instruments, together with his transparent honesty and his elevated conception of the dignity of the physician, his high seriousness and deep respect for his patients, that make him by common consent the "Father of Medicine" and the greatest of

physicians. The greatest scientific name after Hippocrates is that of Aristotle (384-322 B.C.) who gave to medicine the beginnings of zoölogy, comparative anatomy and embryology. A



Colossal bust of Aesculapius  
in the British Museum.

worthy successor of Aristotle was his pupil Theophrastus who was called the “protobotanist” because he did for the vegetable kingdom what Hippocrates had previously done for clin-

ical and surgical medicine, in that he collated the loose plant-lore of the woodmen and rhizotomists into a systematic treatise.

Greek medicine was finally established on a respectable footing in Rome in the personality, tact, and superior ability of Asclepiades (124 B.C.) who was the first to mention tracheotomy. Dioscorides, the originator of the *materia medica*, was a Greek Army surgeon in the service of Nero, and utilized his opportunity of travel in the study of plants. His work is an authoritative source on the *materia medica* of antiquity of which he describes about 600 plants and plant-principles. As Theophrastus was the first scientific botanist, so Dioscorides was the first to write on medical botany as an applied science.

Aretaeus, the Cappadocian, comes nearer than any other Greek to the spirit and method of Hippocrates and, on this account, may be readily appreciated by modern readers. As a clinician, he ranks next to the Father of Medicine for the graphic accuracy of his pictures of disease, of which he has given the classic first-hand account of pneumonia, diabetes, tetanus and diphtheria. The natural history of Pliny the elder (23-79 A.D.) is a vast compilation of

all that was known in his time of geography, meteorology, anthropology, botany, zoölogy and minerology; and is interesting for its many curious facts about plants and drugs, its side



Andreas Vesalius (1514-64).

lights on Roman medicine, and its author's many slaps at physicians.

The ancient period closes with the name of the greatest Greek physician after Hippocrates,

namely, Galen (131-201 A.D.) the founder of experimental medicine. He gave us the four classic symptoms of inflammation; differentiated pneumonia from pleurisy; was the first to mention aneurysm and describe the different forms of phthisis. While Galen was little of an anatomist, he was the first and only experimental physiologist before Harvey. The most commanding figure in European medicine after Galen and before Harvey was Vesalius (1514-1564), who alone made anatomy what it is today—a living working science.

#### THE SEVENTEENTH CENTURY

The seventeenth century was the great age of specialized anatomic research and was notable for a large array of individual discoveries and investigations, nearly every one of which had a physiologic significance. The greatest name in seventeenth century medicine is that of William Harvey (1578-1657) who discovered the circulation of the blood. The lacteal vessels were discovered by Vaselli in 1622.

*The Microscope*—The invention of the compound microscope by Leeuwenhoek in the latter half of the century opened out a new field for

medicine in the direction of the invisible world. The earliest of the microscopists was the Jesuit priest Kircher, who was probably the first to employ the microscope in investigating the causes of disease. Another early worker with the microscope was Hooke, a mechanical genius who anticipated many modern discoveries and inventions. The greatest of the microscopists, however, was Malpighi (1628-94) the founder of histology. Famed in biology for his works on the anatomy of the silkworm and the morphology of plants, he made an epoch in medicine by his investigations of the embryology of the chick and the histology and physiology of the glands and viscera.

#### THE EIGHTEENTH CENTURY

The great Swedish botanist Linneus (1707-78) gave the most concise descriptions of plants and animals in all natural history.

The starting point of modern embryology was the work of Wolff (1733-94) who discovered the Wolffian bodies. With the advent of John Hunter (1728-93), surgery ceased to be regarded as a mere technical mode of treatment and began to take its place as a branch of scientific medicine

firmly grounded in physiology and pathology. As a biologist, Hunter dissected and described over 500 different species of animals.

*Vaccination*—Toward the end of the century



William Harvey (1578-1657).

came one of the greatest triumphs in the history of medicine—the successful introduction of preventive inoculation by Edward Jenner (1749-1823). It had long been a countryside tradition in Gloucestershire that dairymaids who had

## HISTORIC DEVELOPMENT OF IMMUNOLOGY 11

contracted cowpox from milking did not take smallpox, and similar observations had been noted in Germany and France. On learning of this fact from a milkmaid, Jenner early conceived the idea of applying it on a grand scale in the prevention of the disease; and on May 14, 1796, he performed his first vaccination upon a country boy, Thomas Phipps, using matter from the arm of the milkmaid, Sarah Nelmes, who had contracted cowpox in the usual way. The experiment was then put to the test by inoculating Phipps with smallpox virus on July first; and the immunization proved successful, for Phipps did not contract smallpox.

### THE NINETEENTH CENTURY

The modern scientific movement did not attain its full stride until well after the middle of the century. The medicine of the early half was with few exceptions only the stationary theorizing of the preceding age. The descriptions of new forms of disease, and the discoveries of anesthesia (1847) by Thomas Morgan and antiseptic surgery (1867) by Lord Lister were the special achievements of the Anglo-Saxon race.

*Biology*—The advancement of scientific medicine in the second half of the nineteenth century was characterized by the introduction of a biologic view of morphology and physiology; out of which came the sciences of cellular pathology, bacteriology and parasitology, which had in them the charm of novel methods of treatment by means of sera and vaccines. The immense growth of general biology in our time is principally due to the theories of Darwin (1809-82), whose bent toward natural history was set by his boyhood interest in botany and his five years' cruise as naturalist. Darwin's "Origin of Species By Means of Natural Selection" was, perhaps, the most wonderful piece of synthesis in the history of science; and his extraordinary marshalling of facts, in evidence of the "survival of the fittest" by natural selection in the struggle for existence, had a far-reaching influence upon biologic speculation. It created the science of comparative physiology and pathology by pointing to the close structural and functional relationship between human tissues and those of animals and plants.

Huxley's text books on physiology (1866) which passed through thirty editions and those

## HISTORIC DEVELOPMENT OF IMMUNOLOGY 13

on vertebrate and invertebrate anatomy are little master-pieces of their kind. Masters of physiology in the second half of the nineteenth century were Helmholtz, Claude Bernard and Lud-



Antonj van Leeuwenhoek (1632-1723).

wig. In connection with the work of Bernard we may follow the modern developments of the physiology of digestion, of metabolism and of the ductless glands. Recent knowledge of the

relation of the nervous system to the salivary and pancreatic glands is mainly due to the physiology of the Russian school, in particular Pavloff. More than to any one else since the time of Harvey do we owe our present knowledge of the circulation to Ludwig, who was probably the greatest teacher of physiology. The rise of modern medical science is inseparably connected with the name of Virchow (1821-92), the founder of cellular pathology.

In 1867 Lord Lister (1827-1912), aided by Pasteur's discoveries, was enabled to bring to a successful conclusion a long series of researches, and to enunciate the principles of the antiseptic system of surgery.

*Bacteriology*—The founders of bacteriology were Louis Pasteur and Robert Koch; the former being also the founder of the modern practice of preventive inoculation against disease, while to the latter we owe the development of the correct theory of specific infectious diseases. Pasteur (1822-95) is memorable for his work on fermentation (1857), virulent diseases (anthrax and chicken cholera, 1877), and preventive vaccinations (1880), particularly of rabies (1885). Koch (1845-1910) published in Novem-

ber 1877 his methods of fixing and drying bacterial films on cover slips by staining them with anilin dyes. In 1881 he produced his important paper on the method of obtaining pure cultures of microorganisms by the poured-plate method. Klebs (1834-1913) is with Pasteur, perhaps, the most important precursor in the bacterial theory of infection. He saw the diphtheria bacillus before Loeffler (1883) and made solid cultures of bacteria before Koch. Loeffler (1852-) discovered the bacillus of glanders (1882) and established the causal relation of the diphtheria bacillus (1884).

*Immunization*—Meanwhile, real light was thrown upon the unknown problems of immunity by Metchnikoff (1845-), the eminent Russian biologist who, in his studies on inflammation, showed (1883) that certain of the tissue-cells—and particularly the polymorphonuclear leukocytes—were active in the defence of the human body by absorbing the invading bacteria (phagocytosis). His theory of phagocytosis remains a demonstrable fact and establishes the important rôle of cells in the processes of immunity. This process in the hands of Sir Almoth Wright and others was utilized in develop-

ing a more complete understanding of immunity against living microorganisms, and of measuring this immunity by the opsonic index.

In America, bacteriology and pathology have been advanced by William H. Welch (1850-), while Theobald Smith (1859-) has been one of the pioneers in the theories of infectious diseases. In 1885 Smith carried out immunizing experiments in connection with his studies of American diseases of hogs. His work along this line constitutes the first experiments in immunization and was soon followed by the work of von Behring, Roux and others in human medicine.

*Immune Therapy*—About 1890 Pasteur's theory of attenuated viruses was extended to the science of toxins and antitoxins by von Behring (1854-). While working in Koch's Institute with Kitasato, von Behring demonstrated that the serum of animals immunized against diphtheria toxin can be used as a preventive or therapeutic inoculation against diphtheria in other animals through a specific neutralization of the toxin of the disease. After trying out the remedy in man, von Behring began to produce it upon a grand scale (1894) and it soon became

recognized as the specific treatment for diphtheria.

#### THE TWENTIETH CENTURY

The most noticeable thing about twentieth century medicine is the growth of coöperation and the fact that nearly every important advance that has been made is prophylactic—that is, comes within the scope of preventing the occurrence, the recurrence, or the spread of disease. The tendency in all branches of recent sciences, even in zoölogy, sociology, therapeutics, internal medicine, and surgery, has been to pass out of the descriptive into the experimental stage. Loeb (1859-), who is now head of the Department of Experimental Biology in the Rockefeller Institute, has been a brilliant investigator in many branches of physiology. Ehrlich (1854-) has done the most effective work since Pasteur and Koch in the science of infectious diseases, and he has added new territory to the domain of experimental pharmacology and therapeutics by his genius for research and his wonderful industry.

In 1903, Wright and Douglas first determined the direct dependence of phagocytosis upon some ingredient of the blood-serum; and they

further proved that this substance acts directly upon bacteria, is bound by the bacteria, and renders them more easily ingested by the leukocytes. To this substance they gave the name



Marcello Malpighi (1628-94).

“opsonin.” Thus, the gap between the original cellular theory of immunity which ascribed protection and cure to phagocytosis, and the humoral theory which ascribed the chief rôle to

substances in the tissue fluids has been filled with discoveries correlating both processes. Largely through the researches of Wright and Douglas, the presence of opsonins in certain diseases has been taken as a measure (opsonic index) of the resistance of the host, and a technic for detecting their presence and quantity in the tissue fluids has been devised. This technic and the information which it yields is of value in some infections under certain limitations.

Bordet has been a great pioneer in the theory of serology and immunity reactions. He discovered bacterial hemolysis (1898) and, with Gengou, fixation of the complement (1900). He also discovered with Gengou the specific bacillus of whooping-cough (1906), the causal relation of which has been recently demonstrated according to Koch's postulates by Mallory and others (1913). Simon Flexner (1863-) has distinguished himself by his work on the etiology and therapy of cerebrospinal meningitis (1906).

Apart from the work of Bordet, Metchnikoff and Ehrlich, there have been many advances in serology of great practical value: notably, the discovery of agglutination and its application to the diagnosis of typhoid fever (1896) by

Widal and Sicard; the diagnostic use of tuberculin by Calmette, von Pirquet and Moro (1907); Sir Almroth Wright's preventive inoculation against typhoid fever by killed cultures of the bacillus (1900); Abderhalden's enzyme reaction in the diagnosis of pregnancy (1912); and the principle of filterable viruses.

## Chapter II

### BACTERIOLOGY

*Origin*—Several of the philosophers of antiquity surmised the existence of living organisms too small to be seen by the unaided human eye. However, prior to the work of the Dutch microscopist Leeuwenhoek, in the latter part of the seventeenth century, definite ocular evidence for the belief on this point did not exist. Leeuwenhoek (1632-1723) spent many years examining through the microscope a great variety of natural objects and, in the course of his observations, chanced to come across the microorganisms now known as bacteria. He supplemented his observations with drawings, and there is no doubt that he was the first to see bacteria and describe them accurately. Although Leeuwenhoek himself made no medical application of his discoveries, others did so; and the “animalcule” or “germ” theory of disease was promulgated to explain the causation of many morbid conditions then ill understood.

Leeuwenhoek’s observations remained prac-

tically isolated and without fruit for nearly a century. It was not until 1786 that the work of the Danish zoölogist, Mueller, added anything of importance to the knowledge of bacteria.



Edward Jenner (1749-1823).

Mueller succeeded in discovering many structural details of which his predecessors had been ignorant. He succeeded in depicting several kinds of bacteria so accurately that they can be

identified today as belonging to one or another of the chief group forms.

Up to the period of Pasteur's investigations, the rôle played by bacteria in various familiar natural processes—such as putrefaction, decay and fermentation—had been, perhaps, vaguely suspected but had not received conclusive demonstration. The memorable researches of Pasteur upon spontaneous generation and fermentation imparted to the study of bacteria biologic importance that it had not heretofore possessed. Bacteria and kindred microorganisms were shown to be responsible for setting in motion and carrying out many everyday processes, the nature of which had not before been understood. It was almost entirely through the work of Pasteur that bacteria emerged from the relative obscurity as microorganisms chiefly of interest to the professional biologist, and took a conspicuous position in natural science as a group of microorganisms whose activities were full of a far-reaching significance for mankind.

### BACTERIA

Bacteria may be defined as extremely minute, unicellular microorganisms which reproduce

themselves with exceeding rapidity and grow without the aid of chlorophyll. There are such wonderful differences in the conditions of life and nutrition which suit the different varieties that bacteria are found all over the known world. Wherever there is sufficient moisture, one form or another will find certain conditions sufficient for multiplication. The fact that each bacterial variety, possible of cultivation, may grow in distinctive ways upon so-called artificial culture media, has been an immense aid in the differentiation of these microorganisms; for the individual cell of most varieties is so minute that even the highest magnification of the microscope may show little if any morphologic difference between microorganisms which produce distinctly different diseases, or between a pathogenic and non-pathogenic form.

*Shape*—The basic forms of bacteria embrace the sphere, the rod and the segment of a spiral. Although under different conditions the type-form of any one species may vary considerably, yet these three main divisions under similar conditions are constant. (1) The spherical form, or coccus, when seen in the process of multiplication through division, is seldom

thought of as a true sphere. It may be elongated or lancet-shaped as frequently seen in the diplococcus of pneumonia; or biscuit-shaped, where the cocci appear to be flattened against one another, as in the diplococcus of gonorrhoea. Those forms which divide in one direction only and remain attached are found in pairs called diplococci, or in chains called streptococci. Those which divide in any axis are found in irregular grape-like bunches and are called staphylococci.

(2) The characteristic of the rod form, or bacillus, is a straight axis with uniform thickness throughout and flat ends. Sometimes the bacillus has rounded ends. Some, as for example the diphtheria bacillus, frequently are of unequal thickness at different portions.

(3) The spiral form, or spirillum, may be a true spiral in shape or only a segment of a spiral. Here, too, we have large and small, slender and thick spirals.

## Chapter III

### DEVELOPMENT OF IMMUNE THERAPY

The fact that individuals who recover from certain infectious diseases are immune has been known since the earliest times, and was noted by Thucydides in relation to the plague at Athens. In China, practical application of the observation was made as early as 1000 A.D. by exposing children to smallpox or actually inoculating them with dried lymph, in order to produce a mild form of the disease which they usually survived and which rendered them immune. Among certain castes in India and some of the wild tribes of Africa it was the practice to immunize individuals with small doses of snake venom as a protection against subsequent bites. Smallpox inoculation was introduced from Asia among Western nations in the eighteenth century. Inoculations of cowpox as a protection against smallpox had also been practised in England and on the Continent in isolated instances; but it was not until Jenner had made his observations that the value of the method

was established and the procedure generally introduced.

*Pasteur's Achievements*—Further advances in immune therapy were not made until Pas-



Charles Robert Darwin (1809-82).

teur's work, nearly a century later. From his studies on experimental infections, based on Jenner's observation that immunity to small-pox could be produced by attenuated virus, Pasteur concluded that this might be a general law

applicable to other infections. Acting on this theory he was able to immunize fowls against chicken cholera. He also developed methods of vaccinating against anthrax and swine erysipelas, each instance requiring some special method of attenuating the virus. He found that he was able to diminish the pathogenicity of parasites for their natural host, not only by cultivation and preservation under unfavorable conditions, but also by repeated passage through other animals; and that, while passage through some species might diminish the virulence, passage through other species might enhance it and modify the type of disease produced and the length of the incubation period. The attenuation of the rabies virus—which occurs by passage of the virus through rabbits—gave Pasteur a means of combating street rabies, which has a long incubation period, by immunizing the subject after infection. In 1885 after many experiments on animals, he made his first inoculations in man with success; and in 1892, Haffkine developed a similar method of vaccinating against cholera with the living spirilla attenuated by long culture.

*Basis of Vaccination*—All the methods intro-

duced by Pasteur depend on active immunization with attenuated living virus. By this means he was able to control three of the epizoötic diseases prevalent in France, and to reduce the mortality of rabies in man to a minimum; but, unfortunately, it has not been possible to extend the application of this principle materially, and all important advances have since been made with other means of active immunization. Pasteur's method of inoculation is the basis of the various forms of protective and therapeutic inoculation or vaccination in use at the present day, whether the vaccine consists of a living culture of modified virulence, or a suspension of the killed microörganisms, or an extract of pollen grains which are the causative factors of hay fever.

It was shown by Salmon and Smith in 1886, and independently by Chamberland and Roux in the following year, that it was not necessary to introduce living microörganisms in order to produce immunity, but that the same result could be obtained by injecting bacteria killed by heat or, in some cases, by injecting culture fluids from which the bacterial cells had been removed by filtration.

*Vaccine Therapy*—Vaccination by the use of cultures killed by heat or antiseptics was introduced by Kolle in 1896 as an improvement on Haffkine's cholera prophylaxis. In the same



Thomas Henry Huxley (1825-95).

year, Wright introduced the use of killed cultures for immunization against typhoid fever and, two years later, Shiga applied the procedure to dysentery with moderate success. Clowes was the first to report a definite method

of vaccination against hay fever in this country, and his work stimulated extensive study of this form of active immunization which has now been placed on a more complete basis by Koessler.

All of these procedures were prophylactic, but in 1904 Wright introduced active immunization as a therapeutic measure in many chronic infections. He used, for the most part, cultures of the specific microorganism killed by heat and, when possible, prepared his vaccine from strains isolated from the lesion to be treated. Further, he made use of the opsonic index as a means for determining the dosage of his bacterial vaccines. Largely owing to the advocacy of Wright, killed cultures have acquired an important position in the treatment of almost all infections which can be definitely associated with a known type of microorganism.

*Serum Therapy*—Far more marked success from a therapeutic point of view has been obtained by passive immunization. The production of antitoxic sera was made possible by the discovery, by Roux and Yersin in 1889, that the injury caused by infection with the diphtheria bacillus was chiefly due to a soluble toxin which the bacillus produced in culture as well as in the

animal body. The same was shown by Knud Faber (1890) to be true of the tetanus bacillus.

We owe to von Behring the discovery that antitoxic immunity can be transferred from one animal to another by injection of blood-serum from the immunized animal. In 1890 he succeeded in immunizing animals against the tetanus and diphtheria toxins, and in protecting other animals from the fatal results of infection by injecting them with the serum of immunized animals. In 1893 von Behring first introduced his antitoxin for use in human diphtheria. The wonderful results which he obtained have led to innumerable attempts to apply the same principle to the treatment of other conditions; and Calmette, in 1894, developed an antitoxin for snake venom which is fairly effective, while tetanus antitoxin is invaluable in the prophylaxis and treatment of tetanus.

Antibacterial sera have been placed on a basis of approved value by the scientific work of Flexner, who perfected Antimeningococcus Serum (1906) and its rational method of administration by the intraspinal route—thus placing antibodies in direct contact with the infecting bacteria.

**THEORIES UPON WHICH IMMUNE THERAPY  
IS FOUNDED**

The methods of vaccination introduced by Jenner and Pasteur were based on the observation that survival after a modified form of a disease resulted in protection, but they did not analyze thoroughly the nature of this protection. The further application of immune methods has been the result of innumerable investigations into the mechanism of immunity, some of which may be briefly mentioned.

*Phagocytosis*—In 1884 Metchnikoff published the first of a series of observations upon the behavior of certain cells of the lower animals toward insoluble particles that may be present in the tissues of these animals. The outcome of these investigations was the establishment of his well-known doctrine of phagocytosis; the principle of which is that the wandering cells of the animal organism, the leukocytes, possess the property of taking up and rendering inert and digesting microorganisms which they may encounter in the disease. Metchnikoff believes that in this way immunity from infection may in many cases be explained. He believed that immunity was essentially a matter between the

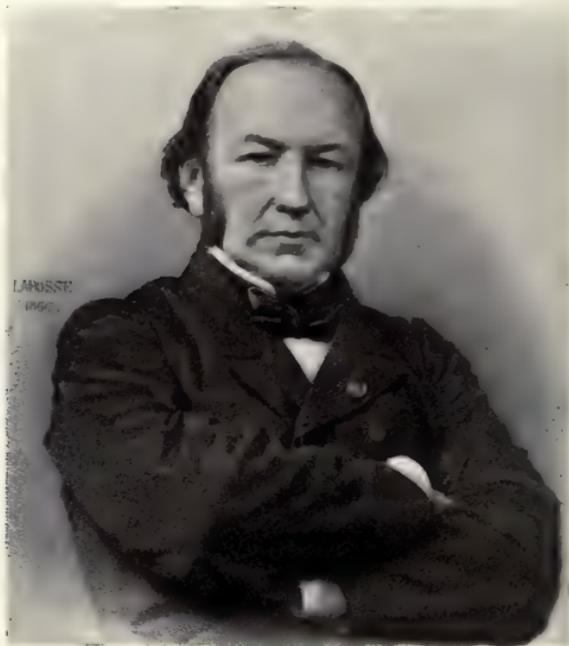
invading bacteria and the leukocytes. Von Behring's discovery in 1890 that antitoxin is a soluble substance present in blood-serum showed the inadequacy of this explanation, and it was soon found that immune serum possessed other specific properties. In 1893 Denys and Leclef showed that even the increased activity of the leukocytes of an immune animal was due to substances in the blood-serum and not to any changes in the leukocytes themselves. Bordet added to the knowledge of bacteriolysis by showing that two distinct substances—amboceptor and complement—take part in the solution of bacteria, either being inactive of itself.

*Side-Chain Theory*—The most important attempt to explain the phenomena of immunity was the so-called "side-chain theory" developed by Ehrlich in 1897. He believed that these phenomena were essentially chemical reactions, and applied to immunity certain ideas which he had developed to account for the combination of food stuffs with tissue-cells. Ehrlich conceives the individual cell to be a complex molecule, comprising a primary central nucleus to which are attached its secondary atom-groups, side-chains, or receptors. Their principal function

is to convert foreign substances into food, which must enter into chemical combination with the central part of the cell to be assimilated. The receptors have, however, a great variety of functions, so that at times they bind the cell to substances that are not foods but actually cell-poisons. Injury to one or more of these receptors, caused by combining with a poison, results in disturbances of the cell-equilibrium and consequent effort of the surrounding receptors at compensating repair. With this liberation of bioplastic energy in the form of an excess of receptors, more receptors are generated than are necessary for the repair of the injury. The excess of these receptors being disengaged from the parent-cell, is thrown into the circulation where it may combine—according to Ehrlich—with the poisons, forming toxin-antitoxin compounds. This excess of receptors free in the serum may be regarded as the antitoxic material of artificially immune animals.

While Ehrlich's theory now seems inadequate in many respects, it has had an extremely important and profound influence on experimental work in immunity. Other theories have since been brought forward to explain the relations

of toxin and antitoxin. Arrhenius and Madson consider that these substances are partly dissociable compounds resembling a weak acid and a weak base, and that the reaction between the



Claude Bernard (1813-78).

two is reversible—their union depending upon an excess of free toxin and antitoxin in the solution. The quantitative relations between the two are thus covered by the law of mass action.

Bordet and Biltz consider the combination not as a true chemical union, but as being of the nature of an absorption phenomenon. More recently, Abderhalden and others have, by the use of polariscopic methods, demonstrated a true disintegration of some toxic substances by immune sera.

*Opsonins* — In 1903 Wright and Douglas pointed out that there are certain substances in sera which so affect bacteria that they are more easily taken up and disposed of by the leukocytes. These substances they termed “opsonins.” Wright and Douglas decided that the amount of opsonins in sera is variable; that these substances are of importance in infection, and can be increased or decreased by injection of killed cultures of bacteria. They express the amount of opsonins present in serum in terms of the phagocytic index of the patient’s blood to the phagocytic index of serum from normal individuals.

## Chapter IV

### TYPES OF IMMUNITY

Immunity may be defined as non-susceptibility to disease or, as the ability to resist the action of the causes of disease.

*Natural Immunity*—Most of the known diseases attack only certain species of animals; other species, even if artificially inoculated, are insusceptible or naturally immune. Among susceptible species certain families and certain individuals also enjoy immunity. The age of the individual sometimes bestows a degree of immunity which is more often relative than absolute. Such insusceptibility, which is congenital or the result of normal growth, is called “natural immunity.”

*Acquired Immunity*—Even in susceptible individuals infectious diseases frequently terminate in recovery, and persons who have recovered are to a greater or less extent resistant to future attacks of the same disease. This condition is called “acquired immunity.”

Acquired immunity may be brought about in

the individual by several means: namely, (1) by recovering from a naturally contracted attack of the disease, as occurs after an attack of scarlet fever; (2) by inoculation with nonlethal doses of the virulent organisms; (3) by inoculation with attenuated virus, as obtains in vaccination against smallpox; (4) by injecting killed bacteria, as in Antityphoid Vaccine; (5) by injecting the specific toxins of bacteria, as in the two exceptional instances of the diphtheria and tetanus bacilli which produce such toxins; and (6) by the injection of blood-serum of animals that have recovered from the disease or that have been immunized by any of the above-mentioned methods, as in the prophylactic inoculation against tetanus with antitoxin. Two types of acquired immunity are recognized and referred to as "active" and "passive."

*Active Immunity*—An individual acquires an active immunity to certain microorganisms when he himself has survived a natural or modified course of the disease produced by infection with this or that particular organism. In this case, the individual produces his own immunity either because he has had the disease naturally or because it has been intentionally and experi-

mentally produced. Experimental, artificial or intentional active immunization is usually called "vaccination", and generally produces in the individual a mild form of the symptoms usually found in the infection. Active immunization, protective and curative, is most frequently attempted with injections of killed bacteria; although toxins and living organisms as well as attenuated viruses are used to immunize against certain infectious diseases. Attenuated or killed organisms prepared for immunization are referred to as "vaccines."

*Passive Immunity*—Acquired passive immunity takes place as the result of the introduction of immunizing substances that have been prepared by actively immunized individuals or animals. This is usually conferred by the injection of blood-serum from immunized animals. There are two classes of immunizing substances: those acting on bacteria are said to be antibacterial; while those acting on toxins are called antitoxic. If the resistance depends on the ability to destroy the invading parasite, it is called antibacterial immunity; whereas, if it depends on the ability to neutralize the toxin of the parasite—the bacterial body itself not being

acted upon—the immunity is said to be anti-toxic.

### ANTIBODIES

Two explanations have been advanced to account for acquired immunity: the humoral theory attributes it to soluble substances in the blood-serum; while, according to the cellular theory, it depends on the activity of phagocytic cells. Whatever may be the essential protective feature, we can demonstrate that when an animal becomes immune its blood-serum acquires new properties which we attribute to the presence of specific soluble substances called immune bodies or *antibodies*.

Any substance which, when introduced into the body can stimulate the production of such antibodies is called an *antigen*. Most antigens are protein substances, and many proteins that are foreign to an animal exercise antigenic powers if introduced into its blood or tissues. It may be an infectious or harmless bacterium, an animal cell, or a toxic or an innocuous protein. Toxins and enzymes of unknown chemical composition, certain glucosides and possibly certain lipoids may also act as antigens.

We infer the existence of antibodies entirely

from the results they produce. They have never been isolated and we do not know their chemical nature; but they are inseparable from one or the other of the serum proteins and may have



Ivon Petrovitch Pavloff (1849-).

the same chemical characteristics. They are unstable compounds, being easily destroyed by heat and by various chemical agents. They are demonstrated and their approximate concentration determined by their reactions with the cor-

responding antigen, either *in vitro* or when transferred to the body of another animal.

*Varieties*—The effect of antibodies on bacteria or cells is more easily observed than are their reactions with soluble substances. Among the immune bodies produced in response to the injection of antigens, we identify the agglutinins, the lysins, the opsonins, and the precipitins, etc. The *agglutinins* cause the cells to clump in masses, a result which does not seem especially protective. The *lysins* disintegrate the cells and bring the constituents into solution; but in order to effect solution of the cells, they require the presence of complement, a substance which is present in normal serum and which is not increased during immunization. Immune bodies of this type, which are inefficient without complement and are thought to act by uniting the complement to antigen, are referred to as *amboceptors*. We recognize that serum produces an invisible change in antigenic cells which enables leukocytes to ingest them, and that this property is increased in immunization. We attribute it to the presence of substances known as *opsonins* or *tropins*. If a soluble antigen is combined with the corresponding immune se-

rum, the formation of a flocculent precipitate can frequently be observed. The antibodies responsible for this phenomenon are called *precipitins* or coagulins. The precipitin reaction is the only directly visible result of the combination of antibodies with soluble antigens, but there is evidence that other changes take place. Another evidence of the action of immune serum is that a soluble toxin combined with the corresponding serum is rendered harmless apparently without disintegration of the toxin. The neutralizing substance merely prevents the toxin from uniting with the tissue-cells, and is called *antitoxin*.

*Source*—It has been found that after injection of antigen, the spleen, bone marrow and lymph nodes show increase of antibodies before the blood which, however, soon gains more and more, while the tissues mentioned gain relatively less. The most natural conclusion would seem to be that the antibodies are formed in the blood-making organs, and the result of splenectomy certainly favors this view. Loss of blood increases the output of antibodies and this also points to the blood-making organs as their source.

*Specificity*—The word *specific* designates a characteristic of the phenomena of immunity that is of fundamental importance. It has been found that a given antibody has a very special affinity for the antigen calling it forth, so that its action is obtained in the most pronounced degree with that antigen. This, in the most general sense, is what “specific” indicates in immunology; and practically all antigen-antibody reactions—both those that occur in the body and those that are observable in the test tube—follow this law of specific action.

## Chapter V

### METHODS OF IMMUNIZATION

*Active Immunization* may be carried out (1) with attenuated virus—the attenuation being obtained by heating, by drying, by passage through animals, or by prolonged cultivation at temperatures above the optimum; (2) with sub-lethal amounts of virulent virus; (3) with killed bacteria, (4) with bacterial products, or toxins, and (5) with extracts of pollen. From a practical standpoint, the first, third and fifth methods only are used and are spoken of as “vaccine therapy.” Active immunization may be practised for two purposes: (1) for the prevention of disease and (2) for the treatment of disease.

#### PROPHYLACTIC ACTIVE IMMUNIZATION

Prophylactic active immunization is accomplished by the production of immunity which is held in reserve to overcome an infection if it should occur. For example, immunity against the virus of smallpox may be produced by inoculation with cowpox virus, so that for several

years the system will be protected against smallpox. Even if vaccination has been delayed until smallpox has actually been contracted, inoculation with cowpox virus early in the period of



Carl Ludwig (1816-95).

incubation so stimulates the tissue-cells that sufficient antibodies are produced to modify and considerably lessen the virulence of the infection, or to entirely prevent the development of

the infection. A good example of protection after infection has occurred is shown in antirabic treatment, in which the Rabies Vaccine is given in such doses and at such intervals that sufficient antibodies are produced to neutralize the effects of rabies virus and to actually destroy it during the period of incubation; that is, during the interval that elapses between the time of infection and the appearance of the symptoms.

#### THERAPEUTIC ACTIVE IMMUNIZATION

Vaccine therapy owes its origin to the researches of Sir Almroth Wright and his colleagues, who originally employed the method for treating those infections that showed a tendency to chronicity and in which true toxins played no part. Wright believes that any stimulus that will arouse the tissue-cells to throw into the circulation substances from the invading bacteria or diseased tissues may result in increasing antibody formation, followed eventually by clinical improvement or cure. Injection into the patient of killed bacteria in sufficient numbers will furnish the stimulus necessary for arousing dormant tissue-cells to produce the antibodies necessary for overcoming

the infection. In other words, with each infection the patient endeavors to protect itself by producing antibodies. When the protection is insufficient, infection will spread; when the antibodies are in excess the infection is overcome; when the forces are about equal, a stage of chronicity may result in which the patient becomes accustomed to the invaders, and while the infection does not spread rapidly it does not on the other hand recede. In chronic conditions, therefore, a dose of bacterial vaccine may excite dormant or inactive cells to furnish an extra quantity of antibodies and thus turn the tide. In therapeutic inoculation, therefore, the fundamental principle is to stimulate in the interest of the infected tissues the immunizing capacities of the uninfected tissues.

In this connection it should be remembered that the usual forms of treatment should be given while vaccine therapy is being instituted. For instance, it is useless to employ a vaccine as the sole means of treating a patient with a suppurative sinus. If an infected suture is directly responsible for the suppuration, the suture should be removed, if possible; and after this is done, a vaccine may be of considerable aid in

overcoming the coincident infection. Likewise, abscesses should be incised and proper drainage of a discharging wound afforded. In other words, any means taken to increase the resist-



Louis Pasteur (1822-95).

ance of a patient to an infection, by developing antibodies, should be supplemented by the best surgical and medical treatment possible for that condition.

*Passive Immunization* is brought about by the introduction of immune bodies or antibodies that have been formed by the tissues of actively immunized individuals or animals and which are contained in their blood-serum. In the practical application of passive immunization, the immunizing process is carried out by the injection into an individual of blood-serum from actively immunized animals. The individual, therefore, receives the antibodies in a passive manner—that is, his tissue-cells are not called upon to produce antibodies. Since blood-serum of an immunized animal contains the antibodies and is the usual vehicle by which they are transferred, the method of passive immunization is called “serum therapy.” Passive immunization may be employed for two purposes: (1) to prevent disease, and (2) to treat disease.

#### PROPHYLACTIC PASSIVE IMMUNIZATION

In prophylactic passive immunization, the antibodies are introduced into the tissue fluids of the individual before infection has occurred, or at least in the early stage of infection in order to augment the natural protective powers of the tissues before the infection has become suffi-

ciently established to produce disease. Since the antibodies may be introduced in a short space of time and in this way quickly induce immunity, passive immunization for prophylactic purposes is indicated when the danger of infection is imminent and when it is impossible to stimulate the individual's tissue-cells to produce his own antibodies by active immunization with a vaccine. Since the antibodies are produced in another animal the serum when introduced into the human body represents a foreign protein, and the antibodies are retained for relatively short periods of time because they are quickly eliminated or destroyed. In active immunization, however, the antibodies are in native surroundings and the tissue-cells of the individual continue to produce them for some time after active stimulation has ceased—thus, often insuring an immunity of long duration. Frequently the two forms are used simultaneously, as the immune serum will afford instant protection while the vaccine is stimulating the tissue-cells to produce antibodies that will increase and maintain the protection for a longer period of time. This method has been used chiefly in experimental and veterinary work.

**THERAPEUTIC PASSIVE IMMUNIZATION**

In therapeutic passive immunization the conditions are somewhat different. During the course of an infectious disease the tissue-cells



Lord Lister (1827-1912).

are actively engaged in combating the infecting bacteria, so that reinforcements in the form of specific antibodies are indicated and welcomed for the aid they give in overcoming the infec-

tion. Hence, the more acute the infection, the greater is the indication for introducing an immune serum. In chronic infections and in some acute infections, we may practise active immunization by introducing a vaccine with the purpose of stimulating dormant cells to produce antibodies; but as a rule it is reasonable to assume that in a severe generalized infection, the tissue-cells are doing their utmost to overcome the infection and an extra stimulation may be actually harmful. By introducing antibodies produced in some other animal, however, practically no extra strain is thrown upon the cells. On the contrary, the tissue-cells may be relieved when the new antibodies overcome the infection, and in this manner an opportunity is afforded the cells to build up the bodily vitality.

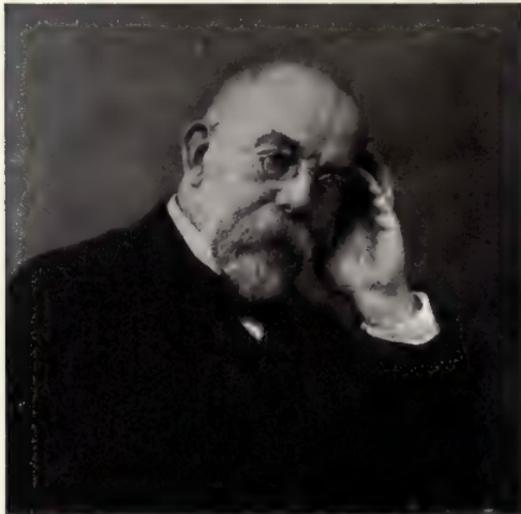
## Chapter VI

### ANAPHYLAXIS AND SERUM SICKNESS

There has been frequent mention in the literature lately of "anaphylaxis" and "serum sickness" in connection with the use of Diphtheria Antitoxin, and it is important to understand these phenomena and their relation to serum therapy. These conditions, however, bear no relation whatever to the antitoxic property itself, but are caused entirely by the foreign proteins contained in the horse serum. They may be produced with normal serum, antibacterial serum, as well as with antitoxic serum.

*Symptoms*—In a small proportion of cases (about 5 to 14 per cent), the injection of horse serum is followed by transitory and not very severe symptoms, which appear only after 5 to 15 days; and consist of skin eruptions usually of an urticarial form, fever, general swelling of the lymph glands, and occasionally pain in the joints. This condition is the so-called *serum sickness*.

If, several months or years later, the patient should be reinjected with horse serum, the symptoms may be reproduced: may be more intense and rapid; and may appear within 3 to 10



Robert Koch (1843-1910).

minutes or at least within an hour after injection. These rapidly appearing and intense symptoms constitute the phenomenon of *anaphylaxis*, and consist of pruritus (manifested by intense itching of the nose), sneezing, hydrorrhea, lacrimation, oppressed feeling, and difficult respiration. Later, slight fever, ma-

laise and general urticaria occur. The urticaria usually does not appear until about the third day. In an extremely small proportion of cases (1 to 50,000, according to Park), the anaphylactic symptoms are characterized by labored respiration, cyanosis, collapse, unconsciousness, and death. The entire picture is an exact counterpart of the anaphylactic shock so readily produced by a second injection of horse serum into the guinea-pig.

*Mechanism*—This phenomenon was first described by Auer and Lewis and is attributed by these investigators to spasm of the smallest bronchioles. This spasm virtually causes suffocation of the animal, inasmuch as air cannot pass either in or out of the lungs. Thus, the phenomenon is not due to any actual poisons in the horse serum, but results entirely from a hypersusceptibility of the individual whose tissue-cells split up the foreign protein of the serum into highly poisonous intermediary products, to which the toxic symptoms are due.

Schultz and Jordan have shown experimentally that serum anaphylaxis is essentially a matter of hypersensitization of smooth muscle in general, and they suggest that the occasional

cases of sudden death in man, following serum injections, may perhaps be due to an abnormal development of the mucous membrane and smooth muscle of the bronchi, as in asthmatics; and, that the smooth muscle, being hypersusceptible, produces asphyxia by sudden contraction.

*Examples*—Anaphylaxis, then—also called hypersusceptibility—is a condition of unusual or exaggerated susceptibility of the individual to certain foreign proteins. The condition may be inherited or acquired, local or general, and is specific in nature. A variety of anaphylactic phenomena occur in man. Many idiosyncrasies with respect to foods—strawberries, cheese, fish, oysters, buckwheat, pork, eggs, cows' milk, etc.—are expressions of anaphylaxis. Striking examples of sensitiveness to cereals, milk, and egg white (egg asthma) have been described in babies and young children. A clinical example of anaphylaxis is the hypersusceptibility of some individuals to pollen, resulting in hay fever. *Most of the cases, however, of horse serum anaphylaxis in man occur in asthmatics or in persons who present a history of asthma or discomfort when about*

*horses.* There is such a condition known as "horse asthma" and individuals who are affected by this condition are unable to withstand the odor about a horse stable.

*Fatalities*—H. F. Gillette collected 28 cases of collapse after serum injection, of which 15 died. There was a common history of previous asthmatic trouble in all but 5 of the 28. Rosenau and Anderson of the Hygienic Laboratory collected some 19 cases of sudden death following the injection of horse serum. These two series of cases are the only ones on record; and when one considers the enormous number of patients who have been injected with horse serum, these 34 fatal cases become insignificant.

*Besredka's Test*—The possibility of anaphylaxis suggests two precautions in serum therapy: (1) Except in urgent cases, avoid giving horse serum to individuals known to be asthmatic, especially those whose symptoms are brought on by being around horses. (2) If hypersusceptibility is suspected, the method of Besredka of the Pasteur Institute in Paris may be applied. In experimenting upon animals, he found that by introducing into the body of an

animal a small dose of the serum to be employed some time before the full dose was injected, he could prevent the development of toxic symptoms. He applies the same princi-



Elie Metchnikoff (1845-).

ples and the same methods to the serum treatment of disease in human patients (*The Lancet*, August 16, 1913, p. 462).

Thus, one or two drops (0.1 c.c.) of the serum may first be injected subcutaneously and, if no toxic symptoms (such as labored respiration, cyanosis, unconsciousness, etc.) appear

after one hour, the individual may be said not to be hypersusceptible. If, after such a test, the individual shows no reaction, or a reaction in which the symptoms consist of mild pruritus, sneezing, difficult respiration, etc., the physician may feel absolutely sure that the injection of the entire dose of serum at the end of an hour will produce no ill effects.

*Precautions*—The risk of serum injection is much less than that attending the administration of many drugs, and should never weigh in the treatment of diphtheria or even in prophylactic injections when exposure to the disease is at all likely. It may, however, have some bearing on the indiscriminate immunization of normal individuals. In patients with a history of asthma or with suspected status lymphaticus, it may be advisable to give a very small test dose and to precede the therapeutic dose with the administration of 0.01 grain of atropin hypodermically.

## Chapter VII

### VARIETIES OF SERA

Sera may be divided into immune sera and normal serum. *Normal Serum* is obtained from the blood of normal animals—that is, animals which have not undergone any intentional process of immunization. *Immune Sera* are fluids containing antibodies already formed and are derived from the blood of animals that have been specifically immunized. For practical purposes the horse is usually employed for the purpose of producing sera. Immune sera from immunized horses are injected into the circulation or into the tissues of man to supply antibacterial elements or antitoxins without stimulating the tissue-cells of the patient to the production of these substances. Therefore, in the use of immune sera, the antibodies formed by the tissue-cells of the horse are supplied to the patient and a condition of passive immunity is established, lasting only a few weeks.

*Action*—There are two varieties of immune

sera: (1) *Antitoxic sera*, and (2) *Antibacterial sera*. The former, represented by Diphtheria Antitoxin and Tetanus Antitoxin, neutralize the toxin in the circulation and in the various



Paul Ehrlich (1854-).

tissues and body cavities. In diphtheria and tetanus, the bacteria elaborate a poison or toxin which is absorbed into the circulating blood and is carried to the tissue-cells. This toxin must be rendered inert before it has been

taken up in too great quantities by those vital tissue-cells which have an affinity for it, in order to effect a cure of the disease. Antibacterial sera, represented by Antipneumococcus Serum, act directly upon the invading bacteria and render them inert or aid in their destruction, thereby arresting the disease.

*Types of Antibodies*—The antibodies in antitoxic sera are chiefly antitoxins, substances which neutralize the bacterial poisons or toxins; while the antibodies in antibacterial sera consist of bacteriolysins, agglutinins, precipitins, opsonins, and other substances, all of which act directly upon the bacteria and aid in destroying them and their intracellular products. In contrast to immune sera, normal serum does not contain any specially induced antibodies, but is used on account of its hemostatic properties.

## Chapter VIII

### PREPARATION OF IMMUNE SERA

The production of immune sera follows along much the same lines for both antitoxic and antibacterial sera. There are, however, three distinct differences in the methods: (1) For the production of antitoxic sera, the solution of toxin is used as antigen with which the horse is immunized, whereas in the production of antibacterial sera, cultures of the specific bacteria are used. (2) In America, antitoxic sera are usually refined and concentrated and the antibacterial sera are not. In order to designate the refined and concentrated product and to distinguish the refined from whole serum which formerly was used, the antitoxic sera are usually termed Diphtheria Antitoxin and Tetanus Antitoxin. (3) The method of standardizing the antitoxic sera differs from that of testing the antibacterial sera, inasmuch as there is a definite and generally accepted unit of immunity established for the antitoxic sera.

*Outline of Method*—In the preparation of

immune sera, the toxin or the culture is injected into a horse in repeated and gradually increasing doses. This process is carried on until the antibodies in the horse's blood have reached a point of maximum concentration. A certain quantity of blood is then withdrawn from the horse and the serum which contains the antibodies is separated from the other constituents.

*Care of Horses*—Various animals have been used for serum production but the horse is generally considered to be the most convenient, most easily managed and, because of its size, yields the greatest amount of blood-serum. All horses must be healthy and vigorous when inoculated and must be kept so by being well fed, well housed and carefully exercised. Horses selected for serum production are subjected to a thorough physical examination by a competent veterinarian and are kept under observation for several days in a quarantine stable. During this period the mallein test is applied to insure freedom from glanders. All healthy horses are then immunized against tetanus by receiving a prophylactic injection of Tetanus Antitoxin.

*Production of Toxin*—The first step in the process of the production of Diphtheria Antitoxin is the preparation of the solution of diphtheria toxin, which is accomplished by growing a culture of the diphtheria bacillus on a suitable fluid nutrient medium. The strain of organism that is selected is noted for its capacity for producing powerful toxin. Most of the diphtheria toxin produced in the laboratories of the world for some years past has been obtained from the same highly toxogenic strain of the bacillus isolated many years ago by Dr. William H. Park of the New York City Health Department. The nutrient medium most generally employed is beef or veal bouillon, with peptone added. This culture medium after being placed in flasks is sterilized by heating, after which it is inoculated with a pure culture of the diphtheria bacillus and kept for a week or ten days at a temperature of 35° C. At the end of that time, the bacteria are killed by trikresol and removed from the toxin solution by filtration. The toxin is then stored and protected from the action of light and heat until required for use. Its strength is determined by finding the least quantity that will kill a

guinea-pig of 250 grams weight in four days, this quantity being termed the *minimum lethal dose* (M.L.D.). The toxin most frequently used for immunization has an M.L.D. of about 0.002 c.c.

*Immunizing the Horses*—After the relative strength of the toxin has been determined it is ready to use for immunizing the horses. Small doses are used at first and are gradually increased at suitable intervals until a large amount of toxin can be tolerated, the object being to establish a condition of hyperimmunization whereby a high concentration of antibodies in the blood is attained. The injections are made subcutaneously, using every precaution to prevent bacterial infection. An injection of toxin is usually followed by a rise in temperature in the animal. This soon passes off and subsequent injections are made at stated intervals. After several weeks' treatment the horse is able to tolerate enormous quantities of toxin sufficient to kill hundreds of unimmunized horses. During the course of immunization a sample of blood is taken from time to time in order to determine its antoxic value.

*The Bleeding*—When a suitable stage of immunization has been reached the horse is bled and the utmost care is taken to attain asepsis: all instruments, vessels, and apparatus are



Jules Bordet.

thoroughly sterilized after approved methods. A sterile canula is inserted into the jugular vein and the blood allowed to flow into large, sterile glass vessels containing sodium citrate

which inhibits clotting, so that a separation of plasma from corpuscles can be accomplished. This plasma is protected with chloroform and placed in cold storage until refined.

The above description in its essential details applies to the production of Tetanus Antitoxin as well as to Diphtheria Antitoxin; also to the production of the antibacterial sera, except that in the latter case the blood is drawn in such a way as to obtain serum instead of the plasma.

*Standardization*—The therapeutic use of the antitoxic sera is facilitated by the fact that they can be standardized according to their power of neutralizing known quantities of a corresponding toxin, and by expressing their value numerically in antitoxic units. Normal guinea-pigs weighing 250 grams are used in the test. Neither the guinea-pigs themselves nor their mothers can have been used previously for testing diphtheria toxin or antitoxin; because it has been shown that a certain degree of immunity may be present in guinea-pigs that have previously been used for testing toxin or antitoxin, and in guinea-pigs whose mothers have been injected with toxin and an-

titoxin mixtures. The standardization is complicated because of the fact that filtered cultures contain substances known as toxoids, which are non-poisonous but which have the power of neutralizing antitoxin. Hence, the ratio between the lethal dose of a toxin and its power to neutralize an antitoxin is not constant. The antitoxin, however, is more stable and uniform in its composition and is used as the standard. In this country, all diphtheria toxin used for testing the potency of Diphtheria Antitoxin is tested by titration with a standard antitoxin furnished by the Hygienic Laboratory of the Public Health Service of the United States Government in Washington.

*Unit*—The unit of Diphtheria Antitoxin was originally defined as the amount which will just neutralize one hundred fatal doses of toxin for a 250-gram guinea-pig. To determine the unit strength of an unknown antitoxin, a standard dose of toxin must be used which, when mixed with the official standard unit of antitoxin, will cause death of a 250-gram guinea-pig in 96 hours. To determine the standard dose of toxin, various amounts of toxin are mixed with one unit of the standard antitoxin and injected

into a series of guinea-pigs. That amount of toxin thus administered which causes death of the guinea-pig in 96 hours is called the L+dose. An antitoxic serum is standardized by mixing graded amounts of it with the L+dose of toxin and injecting the mixtures into a series of guinea-pigs. The smallest amount which suffices to protect the animal for 96 hours is regarded as the *unit of antitoxin*.

*Tests*—Having ascertained the potency of the refined antitoxin solution, sterility tests and safety tests are applied to it. For the safety test, the antitoxin is injected into white mice which are kept under observation for seven days. Sterility tests are carried out by placing some of the antitoxin into sterile bouillon which is placed in the incubator for five days. Absence of microorganisms is indicated by the bouillon remaining clear.

*Refining Process*—In 1905 Robert B. Gibson, working under the direction of Dr. William H. Park in the Research Laboratories of the Department of Health of New York City, perfected a practical method for separating diphtheria antitoxin in a refined and concentrated form from the blood-serum of an immunized

horse. In the following year our laboratories introduced to the medical profession the refined and concentrated Diphtheria Antitoxin, prepared as directed by Robert B. Gibson. By



Emil Abderhalden (1877-).

this process, only those serum proteins which are insoluble in a half-saturated solution of ammonium sulphate and soluble in a saturated solution of sodium chloride are retained; all

other protein bodies are removed. Those proteins which are eliminated do not contain antitoxin and are undesirable in the antitoxin solution.

Later it was demonstrated by E. J. Banzhaf that, if the proteins retained by the above process were heated for several hours at  $57^{\circ}$  C., the solubility of certain inert matter contained therein was so changed that it was insoluble in a saturated sodium chloride solution, while the antitoxic protein remained soluble—thus permitting a further elimination of useless material.

By combining the above methods in connection with our own modification, our laboratories employ a method which is briefly as follows: The citrated plasma is diluted with water, and sodium chloride is added up to  $1\frac{1}{2}$  per cent. This mixture is placed in a water bath at a temperature of  $57^{\circ}$  to  $60^{\circ}$  C., and heated for several hours. Heating the plasma causes a certain non-antitoxic portion of the globulin fraction to become insoluble in saturated sodium chloride solution, which otherwise would dissolve and lower the potency of the refined product. After heating, the antitoxin is mixed

with an equal volume of saturated ammonium sulphate solution which precipitates all the globulins. The solution is filtered; and the globulins containing the antitoxin remain upon the filter paper, while the albumins (non-antitoxic) remain in solution and are discarded. The globulin precipitate is now mixed with a saturated solution of sodium chloride which dissolves the portion of the globulin containing the antitoxin, leaving the non-antitoxic portion of the globulin insoluble. The solution is filtered and the insoluble portion discarded. The saturated sodium chloride solution containing the antitoxic globulin is now acidulated to precipitate the antitoxin, and the suspension is again filtered. The precipitate containing antitoxic globulin is pressed to remove the excess of fluid, and is then dialyzed in a parchment bag against running water until the antitoxin is in solution and the inorganic salts are nearly all removed. The reaction and the salt and protein content are adjusted to make the solution isotonic. After dialysis is completed, as shown by chemical analysis, 0.35 per cent trikresol is added as a preservative. The solution is then ready for potency tests and steril-

ization. Sterilization is effected by filtering through paper pulp and then through a sterilized Berkefeld filter. This filter is made of diatomaceous earth—a fine porous material—which, while it permits the antitoxin in solution to go through slowly, does not allow any bacteria to pass. The solution is then tested for safety and sterility, and confirmatory potency tests are made.

The method gives a concentration of about five times the original potency of the unrefined serum. In practice, it produces fewer symptoms of serum sickness than whole serum, due partly to the removal of non-antitoxic protein and, doubtless, also to the fact that the heating of the serum during the refining process diminishes the power to produce anaphylactic symptoms.

## Part II

### SERUM THERAPY

#### Chapter IX

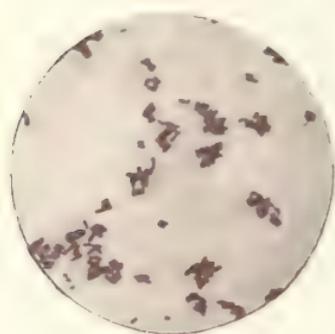
##### ANTITOXIC SERUM THERAPY

##### DIPHThERIA

Diphtheria is an acute infectious disease, caused by the Klebs-Loeffler bacillus which can grow upon any mucous membrane. At the site of their growth, these bacilli generate the toxin which is absorbed by the lymphatics, carried by these to the general circulation and by the blood to all parts of the body.

*Historic*—Diphtheria was known to the ancient Aretaeus, about 50 A.D., who described under the name of "Syrian Ulcer" the characteristic pharyngeal membrane and its extension to the larynx with consequent suffocation. The first great epidemic of diphtheria which can be definitely recognized was described by the Spanish physicians and occurred between

the years 1583 and 1618. In the eighteenth century, diphtheria spread beyond the two southern peninsulas to every part of Europe and North America. Between 1818 and 1821 oc-



*Bacillus diphtheriae*.  
Twenty-four-hour agar  
culture.  $\times 1000$  diameters.

urred the well-known epidemic at Tours, described by Bretonneau. A second epidemic occurred there in 1825-26 and, in Bretonneau's treatise which appeared in 1826, the term "diphthérite" was first used. This was changed by his pupil, Trousseau to

*diphtheria*. Next came the great epidemic of 1855-63 which, so far as can be gathered from historic evidence, was greater than any outbreak since the sixteenth century and differed from the latter in its wide distribution. Between 1855 and 1880 all parts of the United States had been invaded.

Prior to the introduction of von Behring's antitoxic serum in 1893, the mortality from diphtheria was over 50 per cent. Under serum treatment the mortality has been reduced to

less than 10 per cent. The conclusions arrived at by Biggs and Grugard, after a review of a large amount of the statistics and opinions published since the beginning of antitoxin treatment in 1893, were as follows: "It matters not from what point of view the subject is regarded, if the evidence now at hand is properly weighed before one conclusion is or can be reached—whether we consider the percentage of mortality from diphtheria and croup in cities as a whole, or in hospitals or in private practice; or whether we take the absolute mortality for all the cities of Germany whose population is over 15,000, and all the cities of France whose population is over 20,000; or the absolute mortality for New York City or for the great hospitals in France, Germany and Austria; or whether we consider the question with the relation to the day on which treatment of the disease is commenced, or the age of the patient treated; it matters not how the subject is regarded, or how it is turned for the purpose of comparison with previous results, the conclusion reached is always the same—namely, there has been an average reduction of mortality from the use of antitoxin in the treatment

of diphtheria of not less than 50 per cent and, under the most favorable conditions, a reduction to one-quarter or even less of the previous death rate. This has occurred not in one city at one particular time but in many cities and different countries at different seasons of the year, and always in conjunction with the introduction of antitoxic serum and proportionate to the extent of its use.”

#### PROPHYLAXIS

When children or adults have been exposed to diphtheria they may be protected from the disease by the administration of 1,000 units of Diphtheria Antitoxin. This is now the accepted prophylactic dose. The protection is absolute for ten days and usually lasts from three to four weeks. If danger of infection persists longer than two weeks the prophylactic injection may be repeated, inasmuch as antitoxic serum consists of foreign protein and is eliminated from the system rather rapidly. Hence, for prophylactic purposes, it is desirable that the serum be administered subcutaneously—preferably in the interscapular region—so that it will be absorbed slowly and its

immunizing effect persist for a maximum period.

When a person develops diphtheria, all other members of the family should receive at the earliest possible moment an immunizing dose of Diphtheria Antitoxin. Immunization is especially indicated in hospitals, asylums and institutions for children. When an epidemic exists in the neighborhood, it is often wise to immunize the children who attend public schools. The advantages of immunization are best illustrated by the records of the New York City Health Department which shows that out of more than 80,000 cases immunized only 182, or 0.2 per cent, developed diphtheria.

#### TREATMENT

Thousands of lives have been saved by the use of Diphtheria Antitoxin and many more cases of diphtheria could be saved by the early employment of large doses of the antitoxin. Diphtheria being a toxic disease, it is necessary in the treatment to employ large doses of antitoxin as early as possible, in order that the toxin may be neutralized. The dosage will depend upon the apparent severity of the disease

and the time that has elapsed since the onset of the infection. No one can estimate absolutely the amount of toxins that have been and are being absorbed. Hence, there is no positive indication to show the exact dose necessary in any case. The principal thing to do, therefore, is to be sure to give enough antitoxin. The physician can be guided to some extent by the amount of membrane present, its location, the duration of the disease prior to diagnosis, and the general constitutional symptoms, including prostration, condition of the heart, pulse-rate and mental apathy. It is, however, possible to formulate certain rules for determining the dosage.

*Dosage*—The experience of clinicians all over the world, involving many thousands of cases, reveal the fact that the doses of Diphtheria Antitoxin which were first administered when the product was introduced and which are too often used at the present time are quite inadequate to produce the desired effects. It is becoming more and more evident that the initial dose should never be less than 10,000 units, even when the patient is seen in the early stage of the disease. If a case is seen within

the first twenty-four hours with membrane limited to one tonsil, 5,000 units may suffice. Cases with membrane extending to the soft palate and uvula, or to the posterior wall of the pharynx, should always receive 10,000 units as an initial dose. If, in addition, the nose or naso-pharynx is involved, at least 15,000 to 20,000 units should be administered. If there is a considerable amount of membrane, or if the infection is a virulent one, or if the progress of the disease has been rapid, and particularly in all cases of laryngeal diphtheria (croup), it is probably best to employ 20,000 to 25,000 units.

*Value of Large Doses*—The object of giving large doses of antitoxin is to secure the rapid and complete neutralization of the toxin by a single dose of antitoxin. The endeavor should be made to give at once, as an initial dose, such an amount of antitoxin that this neutralization will be accomplished without delay, and to insure there being an excess of antitoxin still in the system to combat toxins later elaborated. To give a dose too small invites disaster by causing delay in checking the diseased process. To give too large a dose can do no harm and

may be a safeguard for the future. The benefits to be derived from large doses of antitoxin through the rapid neutralization of toxins are threefold: (1) complications are minimized; (2) the patient's recovery is hastened and the infectious period shortened; and (3) malignant cases are rendered less severe or even aborted.

*Single Large Dose*—In a recent paper based on personal observation of over 10,000 cases of diphtheria (*The Journal A. M. A.*, Sept. 5, 1914) Dr. S. S. Woody, Chief Resident Physician to the Philadelphia Hospital for Contagious Diseases, stated: "No case of diphtheria, however mild, should receive less than 10,000 units". Dr. William H. Park, Director of the Bureau of Laboratories of the New York City Department of Health, recommends 5,000 units in mild, 10,000 in severe and 20,000 in malignant cases. As a result of long study of the effect of antitoxin on diphtheria, Dr. Park is of the opinion that one dose sufficiently large and administered early is probably sufficient for the whole course of the disease; and he states that two, three or four doses are probably unnecessary and often inadvisable, and calls attention

to the results obtained at the Willard Parker Hospital. He states that during the year 1913, 95 per cent of all cases of diphtheria treated there received but one injection of antitoxin: and the records show that the mortality from the disease has been the lowest in the history of the institution. As a result of his studies, Dr. Park concludes that the first dose should be sufficient for the entire disease, and that further doses should only be given in case one has not judged correctly the amount required in the first dose; and, that while there is no harm in giving additional doses, even if the first is sufficient, there is great harm in relying on later doses to add to the effect of the first.

Some later studies of Schick, which bear on the dosage of Diphtheria Antitoxin in the treatment of diphtheria patients, have recently been reported from von Pirquet's clinic in Vienna. It is interesting to note how closely the results obtained by Schick correspond to those which followed the careful studies of Dr. Park. One of the most important of Schick's observations is that repeated injections of the antitoxin are superfluous and not warranted. The only circumstance in which a second injection is of

value is when the first injection given has been smaller in amount than it should have been.

*Repeating the Dose*—It may be necessary to repeat the dose. The indications for this are: (1) If, after twenty-four hours, the false membrane is spreading or does not show signs of curling at the edges; (2) if the general symptoms are not improved, as shown by the pulse-rate which is the same or increased; (3) the mental apathy being the same or more marked. This latter condition is an extremely valuable guide. In cases where sufficient antitoxin has been given, the improvement in the mental condition is more rapid than that of any other symptom. In croupous cases unless the obstruction is lessened—as shown by the cough being looser, less metallic, and more moist with less dyspnea—the dose should be repeated. In all cases the second dose should be as large as the first. According to Dr. Park, when a maximum of from 20,000 to 25,000 units in a child and 40,000 to 50,000 units in an adult has been reached, it is useless to administer more antitoxin. He states (*The Journal A. M. A.*, September 5, 1914). “Forty thousand units will save any patient that one million will.”

*Difficult Diagnosis*—Physicians are frequently called to see a patient where the diagnosis is not clear at the time of the first visit. It may not always be possible to determine at the first visit whether the case is one of diphtheria, tonsillitis, syphilis or Vincent's angina, and to await the result of a culture means a delay of twenty-four to forty-eight hours. By that time the toxin may have gained such headway as to cause death within a few days, even though antitoxin be used at that late date. The immediate use of antitoxin will shorten the duration of the illness—if it be diphtheria—and, to a very large extent, will lessen the probability of serious complications developing later.

The same is true of croupous cases: whenever the attack does not subside in two to four hours, antitoxin should be given. An early dose will obviate the necessity of intubation if the infection proves to be diphtheria, and will protect the child from the dangers of such treatment. The antitoxin in these cases will not unfavorably influence the course of the disease, if it should not prove to be diphtheria; and danger from undesirable effects from the an-

titoxin itself are very remote in contrast to the beneficial results which will follow if the disease proves to be true diphtheria.

Nasal diphtheria is a form of the disease which too often goes undetected by the practitioner. The infant with persistent snuffles should be regarded as a suspicious case of nasal diphtheria. Such cases are best handled by administering antitoxin at once and taking a culture from both nostrils.

*Deciding on Proper Dose*—When a physician is called to see a case of diphtheria he should diagnose the case comprehensively, taking into consideration the probable virulence of the infection—as indicated by the extent of false membrane and the constitutional symptoms—and the rapidity with which toxic symptoms have appeared after the onset of the disease. Then he should administer a dose of antitoxin which he believes will be sufficient for controlling the entire course of the disease. Second injections should not be required unless the necessary dosage at the first injection has been under-estimated. Therefore, it is far better if 20,000 units are expected or intended to be used in a given case, for the entire amount

to be administered at one dose and as soon as possible after the diagnosis has been made. Any failure of Diphtheria Antitoxin to effect a cure can usually be attributed to delay in its use or to insufficient dosage.

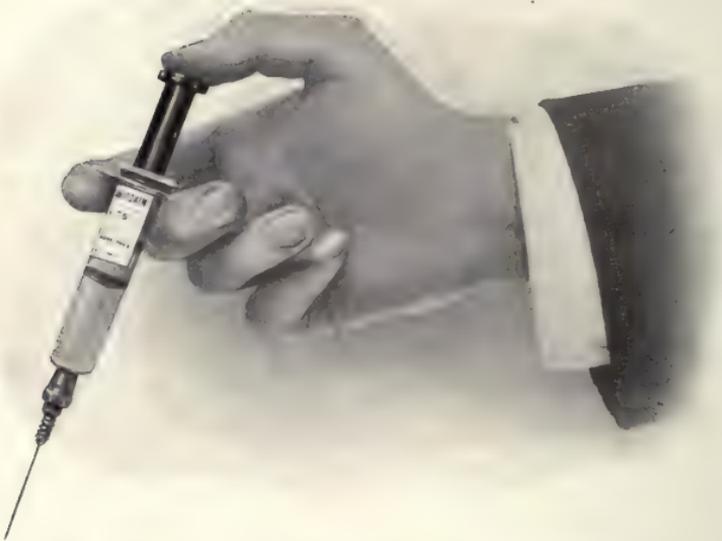
#### EARLY ADMINISTRATION

Many physicians are reluctant to use the large doses because of the expense entailed. The earlier in the disease that the antitoxin is administered, the smaller the quantity of antitoxin that will be required to effect a cure. Therefore, if the practitioner will give one large dose as early as possible in the disease, the necessity for giving several small subsequent doses will be obviated and the actual expense of the treatment will be lessened.

#### METHOD OF ADMINISTRATION

For the treatment of diphtheria, in contrast to prophylaxis, it is essential that the antitoxin be administered by a route which will insure its rapid absorption so that the antibodies will exert their effect as soon as possible. For this purpose it is urgently recommended in severe cases that antitoxin be administered *intraven-*

*ously.* An intravenous injection, placing anti-toxin directly into the blood current, causes an immediate neutralization of all toxin present and, within a few hours, of all toxin in the lymph



An aseptic and ready-to-use type of syringe for administering Antitoxins and Vaccines.

and extra-cellular fluids. During the first twenty-four hours after an intravenous injection, the blood averages ten times as much as in cases in which the antitoxin is given subcutaneously.

According to Dr. Park, *10,000 units given intravenously are worth 100,000 units subcutaneously*. Before using the antitoxin by the intravenous route, it should be very carefully warmed to a temperature of about 98.6°F.—that is, body temperature—by placing it in a water bath. Intravenous injections give the most rapid results and should be used especially in all malignant cases. Moreover, if only a small amount of antitoxin is available when treating any type of diphtheria, the antitoxin should by all means be administered intravenously.

In case the physician does not care to use the intravenous route, the antitoxin should be administered *intramuscularly*, preferably in the gluteal region. The gluteal muscles are abundantly supplied with blood vessels and the antitoxin will be quite rapidly absorbed from that region. *When injected into the muscle, the antitoxin is absorbed about three times as rapidly as when given subcutaneously*, so that the major portion is absorbed within twenty-four hours. Morgenroth and Levy (*Zeitsch. f. Hyg. u. Infect. Dis.*, 1912, LXX; 69) found that the highest antitoxic value naturally occurs after in-

travenous injections, yet, after eight hours, the concentration appears to fall; while with intramuscular injections, after eight hours, the antitoxin content of the blood is nearly as great as immediately after intravenous injection.

*Value of Intramuscular Injections*—Rolleston and Macleod (*British Journal Children's Diseases*, July, 1914) believe that intramuscular injections deserve to supercede all other methods of administration of antitoxin in the treatment of diphtheria for the following reasons: (1) It is quite as simple as the subcutaneous method, insures much more rapid absorption, and is less painful; (2) it is superior to the intravenous method, not only in the great simplicity of its technic, but also in the less rapid excretion of antitoxin after injection; (3) the more rapid absorption of antitoxin by the intramuscular route is shown, not by the effect on the faucial or laryngeal process but by the lesser incidence of paralysis.

*Futility of Subcutaneous Route*—A subcutaneous injection is not wholly absorbed for three days; the water holding the antitoxin in solution is quickly absorbed, but the antitoxin

is held back. The rate of subcutaneous absorption is shown in the following table by Park:

10 per cent in 6 hours,  
35 per cent in 24 hours,  
65 per cent in 48 hours,  
100 per cent in 72 to 96 hours.

The slowness of absorption of antitoxin injected subcutaneously is very evident from this table, showing as it does that it requires forty-eight to seventy-two hours for the absorption into the blood of the greater part of the antitoxin. This in severe cases may be a fatal delay.

#### TREATMENT OF LATE CASES

In hospital practice many patients do not receive the first dose of antitoxin before the sixth or seventh day, or even later, owing to the fact that in most of the cases admitted the disease has reached the advanced stage. In such advanced cases and in septic cases, which have been ill six to seven days and with necrotic membrane of extremely foul odor, Diphtheria Antitoxin may be given in enormous doses, ranging from 20,000 to 50,000 units, and should be given intravenously.

## TETANUS

*Historic*—Tetanus is an acute infectious disease caused by the toxin of the *Bacillus tetani*, and is characterized clinically by painful muscular spasms affecting first the muscles of the jaw and neck and extending in severe cases to the muscles of the body. It is a disease which has long afflicted man, for the symptoms are clearly described in the writings of Hippocrates. In 1885 Nicolaier discovered the *Bacillus tetani* and in 1889 Kitasato obtained the bacillus in pure culture. Finally in 1892, von Behring and Kitasato worked out an effective method of preparing a specific antitoxin.

*Toxin*—The toxin of the *Bacillus tetani* acts directly upon the central nervous system. As in the case of diphtheria, the toxin of tetanus is produced in some local lesion in which the growth and multiplication of the specific bacterium takes place. Experiments by Doenitz and Heymans have shown that the tetanus toxin has a strong affinity for nerve tissue—fixation of the toxin being complete within a few minutes. According to Ehrlich, the affinity between the toxin and the antitoxin is comparatively weak, about 40 minutes being required before

the toxin is completely neutralized. Although the toxin is carried in the blood stream, a large amount of it is taken up by the nerve endings near the infected tissue and makes its way along



Bacillus tetani with  
spores in distended ends.  
× 1,100 diameters.

the nerves to the motor cells of the spinal cord and brain. Not until the action of the toxin on the nerve tissue has already been exerted and pathologic effects produced, do symptoms of tetanus appear.

*Wounds* — Tetanus may be regarded almost solely as a wound complication, but all wounds are not liable to this complication even though tetanus spores be present. Punctured, lacerated and contused wounds are more susceptible than clean-cut or superficial wounds. In the investigations of Andres and Morgan, it was found that the majority of cases occurred from severe contusions with penetration of foreign bodies. These researches also corroborated the accepted view that the common sites

of infection are the extremities, notably the hands and feet. Many traumatism—such as blank cartridge wounds and other Fourth-of-July injuries, gun-shot wounds, nail punctures, machinery wounds, crushes, and other injuries in which dirt is carried into deep wounds—are more or less liable to be followed by tetanus. The danger is especially great when the dirt is ground into the injured tissues; street dust and garden soil being particularly apt to contain tetanus spores.

*Localities*—In many localities the danger is much greater than in others. The sections of the United States in which tetanus is most frequent are northern New York along the Hudson Valley, Brooklyn and the surrounding districts of Long Island, southern Pennsylvania, Virginia, Georgia, Louisiana, Indiana, Illinois and southern California. Where tetanus is prevalent, the horse manure is generally infected as the tetanus bacilli grow in the intestines of this animal and the spores remain alive in the dirt for years.

#### PROPHYLAXIS

Tetanus Antitoxin is a valuable, reliable and efficient preventive against the development of

tetanus. Its use, however, must be thoroughly understood in order to achieve satisfactory results. It must be administered before the advent of symptoms of the disease; for, after the tetanus toxin has combined with the motor nerve cells in the central nervous system, it cannot be displaced or neutralized with antitoxin.

*Reliability of Antitoxin*—The reliability of Tetanus Antitoxin as a prophylactic measure is admirably shown in the statistics published by H. J. Scherck, Chief of the St. Louis Health Department (*The Journal A. M. A.*, 1906, XLVII, 500), in which he reported a series of 291 injuries by toy pistols and other Fourth-of-July injuries. These cases were immunized with Tetanus Antitoxin and not a single person developed tetanus. This series of cases extended over a period of three years, and a comparison of these results with those obtained in another year when no antitoxin was used showed that nearly one-third of the injured succumbed to tetanus. Moreover, it has been conclusively shown that when the antitoxin is injected as late as 96 hours after the injury, it proves a reliable prophylactic against the development of the disease. It is the custom at many dispensaries

in New York City and elsewhere to immunize all Fourth-of-July wounds by injecting Tetanus Antitoxin and, according to Park, none of these cases has ever developed tetanus.

*Dose*—The immunizing dose agreed upon by a committee of American bacteriologists as sufficient to protect against the development of tetanus within the incubation period, is 1500 units of American standard. The antitoxin should be administered subcutaneously, preferably in the interseapular region, so that it will be absorbed slowly and the immunity persist for a maximum period. It is important to remember that a large percentage of the antitoxin is eliminated from the system in the course of about ten days. Hence, in cases where the wounds are extensive, and where it is impossible to thoroughly cleanse the wounds, it is advisable to give a second prophylactic injection at the end of ten days.

*Surgical Care*—The immediate radical cleansing of wounds in which there is ground for suspecting that tetanus may develop is of the highest importance. The surrounding parts should be thoroughly cleaned with soap and water and the wounded tissues cleansed with sterile salt

solution. The wound ought to be widely opened by free incision, if necessary, to thoroughly cleanse the wound and for the removal of foreign substances. Under certain circumstances, excision of the wound is to be advised. Foreign material may be removed with sterile forceps. Friedrich recommends total excision of the focus and foreign body. Ashhurst recommends that the wound be irrigated with hot peroxide of hydrogen, swabbed out with 3 per cent alcoholic solution of iodine, and loosely packed with gauze soaked in the same solution.

#### TREATMENT

It is unfortunate that many physicians have never seen a case of tetanus, and it is also unfortunate that physicians of wide experience are too often inclined to delay the treatment of a suspected case until they are positive of the diagnosis. Such delay has caused many lives to be lost, which otherwise might have been saved by an earlier use of Tetanus Antitoxin. The treatment of tetanus has two distinct purposes: (1) the neutralization of the tetanus toxin, and (2) the sustaining of the patient and the alleviation of the symptoms until the effects of the specific poison subside.

*Mortality Lowered*—Statistics showing the results of the treatment with antitoxin are far from convincing. The mortality of tetanus treated symptomatically is estimated by most observers at 78 to 90 per cent. Tetanus is a disease which presents so many variable factors influencing the prognosis that the evaluation of Tetanus Antitoxin is a matter of considerable difficulty, and many experienced clinicians have doubted whether the results obtained from its use have been any better than those obtained from symptomatic treatment. A study of the mortality statistics of many hospitals shows that too often this skepticism has been well founded. Opposed to this pessimistic view are the reports of a number of small groups of carefully observed cases, such as those of Ashhurst and John, in which the evidence seems strong that antitoxin deserved large credit for the recovery of the patients. Permin has collected statistics in Denmark of the mortality of tetanus treated with and without antitoxin, and he found a mortality of 78.9 per cent in cases treated without antitoxin, as compared with a mortality of 57.7 per cent in cases receiving antitoxin. In a recent paper (*Journal Infectious*

*Diseases*, September, 1914), Dr. E. E. Irons reported the analysis of 225 cases of tetanus treated during the years 1907 to 1913. The cases included those treated in large metropolitan hospitals and those in the private practice of physicians. The analysis was made to ascertain what results are being obtained in this country with Tetanus Antitoxin, and to determine whether the failures in some cases may not be ascribed to the faulty and insufficient method of giving the antitoxin. Irons concludes from this analysis that *the mortality from tetanus is 20 per cent lower when treated with antitoxin than when antitoxin is not used, and that the mortality of cases treated by efficient methods and adequate doses is considerably lower than that of cases receiving small doses subcutaneously.*

*Practical Value of Antitoxin*—It cannot be denied that this is not a brilliant showing for antitoxin treatment, but it is by no means surprising to those who are familiar with (1) the difficulty in impressing physicians with the supreme importance of early treatment, and (2) the frequency with which antitoxin is administered by the least efficacious method, namely,

subcutaneously. More recently, Park and Nicoll (*The Journal A. M. A.*, July 18, 1914) conducted a series of experiments on guinea-pigs which were inoculated with tetanus toxin and then treated with antitoxin when symptoms of the disease became well marked. They showed that the animals practically never survive even when huge doses of antitoxin are given subcutaneously, and but rarely when such a dose is given in the circulating blood; that they do survive in a large majority of cases, even when a fractional amount of antitoxin is given intraspinally. In other words, that *the intraspinal method of administering Tetanus Antitoxin is the only reliable manner in which the animals can be saved*. Subsequently, Park and Nicoll applied the intraspinal method of administering antitoxin in nine cases of clinical tetanus, all of which recovered. The result in this small series is in such markedly favorable contrast to that in a much larger number of cases in which antitoxin was administered by other methods, that there can be no reasonable doubt—especially when the results of experimental work are also considered—that *the intraspinal method of treatment should be given*

*the preference over all others.* The container shown on page 107 has been especially devised for administering the antitoxin intraspinally by the gravity method.

*Dosage*—The following recommendations by Park and Nicoll for the treatment of tetanus are practically identical with those of Ashhurst and John, and seem to be amply justified: “In every case strongly suspected of being tetanus, from 3,000 to 5,000 units of Tetanus Antitoxin should be given at the first possible moment intraspinally, slowly by gravity and always, if possible, under an anesthetic. In order to insure the quickest possible neutralization of all toxins in the tissue fluids, it would seem advisable to give at the same time a dose of 10,000 or 15,000 units of antitoxin intravenously. It is usually advisable to repeat the intraspinal injection in 24 hours. Three or four days later, a dose of 10,000 or 15,000 units given subcutaneously will insure a continuance of a highly antitoxic condition during the next five days. We do not believe there is any advantage in giving larger amounts of antitoxin than those indicated.”

When for various reasons Tetanus Antitoxin

cannot be given in the spinal canal, it is far better to inject it at the earliest possible moment intravenously than to lose time in seeking skilled advice in order to give it intraspinally—which however, should be done as soon as possible. That Tetanus Antitoxin properly used may save the life of a patient in whom tetanus has already developed should be more generally recognized, and the antitoxic treatment should be employed in every case at the earliest possible moment. Every hour lost before giving the antitoxin decreases the chance of saving life. By no means every case will recover, but certainly more can be saved than have been in the past; and there is every reason to anticipate that with the proper use of antitoxin a mortality considerably lower than the present will be obtained.

*Supplementary Treatment*—This use of antitoxin in no way replaces other necessary and recognized non-specific methods of treatment in tetanus. Surgical treatment of the site of infection should be instituted at once. Ashhurst and John recommend that the wound be irrigated with hot peroxide of hydrogen, swabbed out with 3 per cent solution of iodine and

loosely filled with gauze soaked in the same solution. The patient ought to be placed at rest in bed in a quiet darkened room, with competent nursing facilities; and should receive sufficient sedatives to control convulsions, together with adequate supply of fluid nourishment and attention to the elimination by kidney and bowel. Rectal feeding may be resorted to and, in the nutrient enemata, effective doses of chloral and bromides may be administered at appropriate intervals. Chloral and *cannabis indica* are also used with good results to afford relief from painful muscular rigidity and convulsions. For rapid action, paraldehyde and ether suspended in saline and administered intravenously may be used.

#### METHOD OF INTRASPINAL ADMINISTRATION

The technic includes that required for performing a lumbar puncture, and the antitoxin is introduced into the spinal canal *after* the withdrawal of cerebrospinal fluid.

The patient is first etherized and then placed on the side, with head bent forward and knees drawn up. The skin, in the lumbar region of the back is painted with iodin, or washed with

soap and water and followed by alcohol and ether. The operator, whose hands have been sterilized, takes the sterilized needle with its contained stylet in his right hand and introduces the needle through the intervertebral disc between the third and fourth lumbar vertebrae, and a little to one side of the median line; the thumb of the left hand being placed between the spinous processes as a guide. *The point for inserting the needle* may be conveniently located by placing the index and third fingers of the left hand on the highest points of the iliac crests. The middle finger will then rest on the third lumbar spine, and the point of election is midway between this spine and the one immediately below it. The needle should be cautiously pushed forward until the slight resistance of the dura is felt; this occurs at a depth of about two centimeters ( $\frac{3}{4}$  inch) in infants, and at 4 to 6 centimeters ( $1\frac{1}{2}$  to 2 inches) in adults. If bony resistance is encountered, withdraw the needle slightly and change the angle of insertion. As soon as the dura has been punctured, the stylet should be withdrawn and as much cerebrospinal fluid allowed to flow from the needle as possible.



Complete outfit for intraspinal administration  
of Tetanus Antitoxin.

After the fluid has been withdrawn, the glass cylinder is attached to the needle *which is left in position*; and the antitoxin, having been gently warmed to body temperature, is allowed to flow

into the spinal cavity by gravity. (*Care must be exercised not to heat the antitoxin above 98.6° F, otherwise it may coagulate!*) The adjustment of glass cylinder to needle is effected in the following manner:

Withdraw the soft cotton cord from the rubber tubing (the cord prevents collapse of tubing while in the package); remove one of the rubber caps from the glass cylinder and slip rubber tubing over the exposed end of cylinder. Hold the cylinder vertically and remove rubber cap from upper end of cylinder until antitoxin escapes from the metal tip of rubber tubing (thus expelling all air from tubing); then replace the cap and firmly insert the metal tip of rubber tubing into hub of needle. Now remove the rubber cap from upper end of glass cylinder, and adjust the rubber portion of rubber-and-glass union to exposed end of the glass cylinder. (The cotton filter, in glass portion of union, prevents any foreign matter from gaining access to, and contaminating the antitoxin.) *From 10 to 25 minutes should be allowed for the antitoxin to be introduced into the spinal canal.* The flow may be increased or decreased by raising or lowering the glass cylinder. If

any difficulty is experienced in starting the flow of antitoxin, the operator may blow gently in the top of glass tube containing the cotton filter. The physician is enabled to observe, by means of the short glass tubing near metal tip of rubber tubing, the instant that all of the antitoxin has been introduced; and thus air can be prevented from being forced into the spinal canal.

When the desired amount of antitoxin has been introduced, the needle with the attached glass cylinder is rapidly withdrawn and the puncture wound is sealed with collodion.

Note: This equipment may also be used for the intravenous administration.

# Chapter X

## ANTIBACTERIAL SERUM THERAPY

### ANTIBACTERIAL SERA

*Indications*—Antibacterial sera are especially indicated when the patient's vitality is low: when the resisting power of the patient is such that his tissue-cells cannot produce sufficient antibodies to successfully cope with the infection. The practical application of specific antibacterial sera in the treatment of various infections has been used on a large scale. It has been found that by the early injection of serum, the natural resistance of infected individuals can be augmented and the disease materially ameliorated and its course shortened. Even in desperate cases, injections of large quantities of an antibacterial serum have yielded most unexpectedly favorable results, while small doses in similar cases have usually been without beneficial action.

*Reasons for Failure*—In general, however, the results of the use of antibacterial sera in the treatment of specific diseases have not al-

ways been as satisfactory as those obtained with specific antitoxic sera. The chief reasons for failure are: (1) It is not possible to accumulate antibodies in the sera of animals immunized against bacteria in a concentration as efficient as the antibodies in sera of animals immunized against toxins; (2) it has been impossible to adjust the dosage by any accurate unit and the doses which have generally been used have doubtless been too small to produce the desired favorable results; (3) because of the lack of appropriate tests for standardization, inert sera probably have been placed on the market. Up to the present time, no universally accepted unit of immunity has been applied to the antibacterial sera. However, in our laboratories, the therapeutic activity and antibody content of the serum obtained from each immunized horse are determined as accurately as possible by certain laboratory methods, including the complement fixation test and the estimation of the opsonic index. (See Part III). These tests prevent an inert serum from at any time being marketed. Without such tests, sera without any value whatever might be and probably have been marketed, and this doubtless ac-

counts for many of the failures and adverse criticisms connected with some of the antibacterial sera. In addition to the above tests, rigid bacteriologic and physiologic tests are employed to establish the safety of each lot of serum.

*Polyvalent*—It has been demonstrated that different cultures of the same species of bacteria vary widely in their biologic properties. Hence, it is essential in preparing antibacterial sera that the horses be inoculated with a number of different races of the specific bacteria, in order to produce a polyvalent serum which will be efficacious against practically all the races of that type of bacteria likely to be encountered. *Polyvalent* means, therefore, that the serum is prepared from several cultures of the same species of bacteria obtained from many different sources of the same type of infection. The antibacterial sera prepared by our laboratories are all polyvalent sera.

*Antitoxic vs. Antibacterial Sera*—It may be well here to point out the difference between antitoxic sera and antibacterial sera: (1) Antitoxic sera neutralize the toxins or poisons produced by the diphtheria and tetanus bacilli, and

exert no effect upon the bacteria themselves. Antibacterial sera act directly upon the invading bacteria and render them inert or aid in destroying them. (2) Antitoxic sera are used in two diseases only, namely, diphtheria and tetanus; while the antibacterial sera are used in a variety of infective conditions, namely, pneumonia, scarlet fever, erysipelas, septicemia, puerperal sepsis, meningitis and gonorrhoea. (3) The antitoxic sera are used both for prophylaxis and treatment, while antibacterial sera are usually used only in treatment.

#### ANTIPNEUMOCOCCUS SERUM PNEUMONIA

*Historic*—Acute lobar pneumonia, because of its striking and characteristic clinical picture, has been recognized since the earliest times and has always been an uncertain and treacherous disease at any age. Evidently, what we now know as croupous pneumonia was known to the earliest medical writers including Hippocrates, who with others described it with considerable accuracy as peri-pneumonia. Hippocrates said of it that it was “a disease quickly fatal and characterized by sputa of various colors.” The

infectious nature of pneumonia was first advocated by Juergensen in 1872. The discovery of the pneumococcus may be attributed to Sternberg and to Pasteur, who published almost simultaneously accounts of the lance-shaped diplococcus, found in the normal mouth, which was able to induce a fatal septicemia in rabbits. They, however, did not associate the organism of the mouth with the various pathologic lesions which we now know to be caused by the pneumococcus, and it was only after the thorough studies of Fraenkel and of Weichselbaum that the constant association of the pneumococcus with lobar pneumonia was satisfactorily determined.



Pneumococcus in peritoneal pus. Stained with fuchsin. Clear spaces indicate capsules.  $\times 1,000$  diameters.

Sir Herman Weber in England, Juergensen in Germany, Rodman and Austin Flint in this country were pioneers in establishing our modern conception of pneumonia.

*Prevalence*—Lobar pneumonia is an endemic and general sporadic disease that is common throughout the United States and Canada. It is frequent all over temperate Europe and in the inhabited portions of the South Temperate Zone, such as Australia, parts of South America, and in South Africa. Although it is much less frequent in the tropics, it is often seen even there among the inhabitants of the plateau regions. The disease exhibits very marked exacerbations during certain years. The majority of cases occur between November and June, which is supported by the findings in 34,587 collected cases. Accounts of supposed pneumonia epidemics go back nearly as far as written history itself. An extensive tabulation has been made by Wells, who gives a list of epidemics extending back to 1440. It is supposed by some that the plague of Athens, which destroyed one-fourth of the population, as well as the Black Death which ravaged Europe during the middle of the fourteenth century, were forms of pneumococcus infection.

In the United States during the census year of 1900, over 10½ per cent of all deaths were due to pneumonia. Reports published in different

parts of the world indicate that the frequency of pneumonia is steadily increasing. Among the possible reasons which may account for this are: (1) Increased use of alcohol; (2) increased facilities for travel; and (3) increased overcrowding in the home, workshop and places of amusement. It may be conservatively stated that the frequency of pneumonia is at least not diminished.

#### SERUM TREATMENT

*Historic*—Pneumonia was one of the first diseases which engaged attention through serum therapy. The Klemperer Brothers (1891) were pioneers in the field of serum treatment of pneumonia. Until Roemer in 1902 commenced a series of studies of pneumococcus immunity, the treatment of pneumonia by a serum was not seriously considered by the profession. Roemer holds in favor of the success of serum treatment of pneumonia because of the fact that in no acute infection are protective bodies so promptly formed in the blood as in this disease. He states: "Just as the antimeningococcus and antistreptococcus sera, so has the antipneumococcus serum a just claim for recognition and this it will acquire for itself."

*Reasons for Failure*—It is now over twenty years since the first attempts were made to treat a patient suffering from acute lobar pneumonia by means of a serum. Although it has been impossible to demonstrate any marked lowering of mortality in a large series of cases, yet certain clinical observers have felt that in certain instances the results were striking. According to Dr. Rufus Cole, one reason why Antipneumococcus Serum has not been more efficacious in the past is that it has been administered in too small doses. Experiments by Dochez have shown that there is a maximum degree of infection against which no amount of serum, however large, is able to protect. This suggests that, in order to obtain best results from the serum, it should be administered early before the infection has reached too extreme a grade beyond which no amount of serum can be effective. These experiments also afford a possible explanation as to why in certain cases serum seems to have absolutely no effect. According to Forchheimer, there are cases of pneumonia in which no therapy is of use: these cases are fatal from the beginning, being overwhelmed by toxemia and associated infiltration.

*Action of Serum*—Antipneumococcus Serum places antibodies in the blood stream at once and combats the invading bacteria, leaving the patient's tissue-cells free to build up vitality. The serum exerts an abortive influence, for the temperature falls rapidly and by lysis instead of by crisis and the course of the disease is shortened. There is also a change in the physical signs which indicate resolution. The most marked value of this serum is obtained when it is administered early and in large doses.

*Dosage*—In the treatment of pneumonia with Antipneumococcus Serum, relatively large amounts of the serum are administered. The treatment as recommended by clinicians who have reported the most favorable results is to inject 200 c.c. intravenously as the initial dose in adults. (If the subcutaneous route is preferred, 100 c.c. are given in each side of the anterior abdominal wall.) This dose is followed in 12 to 24 hours by 100 c.c., and this amount is to be repeated every 12 hours as long as the temperature remains above 103 degrees. If the temperature falls below 103° and the patient improves, injections of 50 c.c. may be given daily until the temperature falls to practically

normal. The initial dose for children should be 100 c.c. The earlier in the disease that the serum is employed the more favorable will be the results: improvement being indicated by the temperature, physical signs and other clinical symptoms. The outfit illustrated on page 120 has been devised to furnish a convenient means of administering the recommended large doses of Antipneumococcus Serum and other antibacterial sera.

*Intravenous Administration*—The importance of the intravenous method of administration, especially in severe cases of pneumonia, cannot be too strongly emphasized. Dr. Rufus Cole, Director of the Hospital of the Rockefeller Institute, whose extensive experience makes him a recognized authority in this country on the treatment of pneumonia, employs 100 to 500 c.c. of this serum, diluted one-half with salt solution, injected intravenously. In his published report of a series of cases (*The Journal A.M.A.*, August 30, 1913), Dr. Cole states: “The conclusion seems justified, therefore, that one large dose of serum given intravenously is sufficient to sterilize the blood. The results obtained, therefore, from the clinical and labora-



Convenient outfit for administering large doses  
of Antibacterial Sera.

tory studies of this series of cases of pneumonia treated by the injection of large amounts of appropriate serum, seem to indicate that a method

has been devised for the successful specific treatment of cases of acute lobar pneumonia." In his report of 23 cases of pneumonia treated with Antipneumococcus Serum (*Collected Studies from the Bureau of Laboratories, New York City Department of Health, 1913*), Dr. W. R. Williams states that as much as 300 c.c. of the serum were injected intravenously with good results.

*Results.*—Dr. Cole reports that all of the patients seemed to feel better following the injection of the serum and, in a number of cases, the apparent lessening in the degree of intoxication was very manifest. After most of the injections a reaction occurs; the temperature usually rises and then falls but does not necessarily remain low. In some cases the rise of temperature has been marked: in others, the rise of temperature following an injection has been only a degree or so. In all except fatal cases, the serum had an ultimate favorable effect in lowering the temperature and shortening the course of the disease.

Dr. Roland G. Freeman was one of the first clinicians to use large doses of the serum. His report (*American Journal Diseases of Children*,

December, 1912) of a series of children, ranging from 2 months to 3½ years of age, showed that there was an important change in the appearance of the child after the injection of the serum. The children became brighter, took their feedings better, and seemed much improved; and there was a rapid reduction in temperature after the introduction of the serum. Dr. Freeman states: "Serum injections apparently affect favorably the course of the disease and in most cases there appears to be a better reaction on the part of the child after serum injection than before."

In reviewing the work done on serum therapy of lobar pneumonia, one sees a continuous progress in the efficiency of the methods of production and administration of Antipneumococcus Serum. In the earlier observations but little attention was paid to potency of the serum or to the characteristics of the bacteria employed in its production. The doses administered and the method of application were probably inadequate in a majority of instances. Neufeld and Haendel (*Berliner klin. Wochenschr.*, 1912, 680) emphasized the importance of paying attention to the strains of pneumococci used for

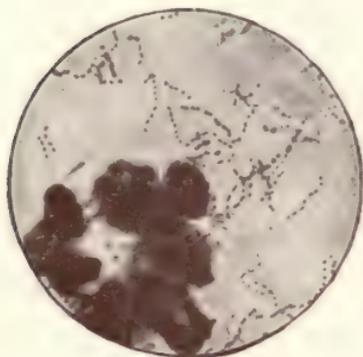
the immunization of animals, and the importance of giving a sufficient amount of serum intravenously to effect the proper concentration of immune bodies in the blood.

#### ANTISTREPTOCOCCUS SERUM

*Scarlet Fever*—Scarlet fever, erysipelas, smallpox, puerperal sepsis and septicemia form a group of diseases in which the streptococcus plays either a primary or a secondary rôle. Accurate knowledge of scarlet fever was obtained in the seventeenth century when Sydenham described it in a manner which permits its easy recognition as the scarlet fever of today. It pervaded the Old World everywhere, having been recognized in England in 1861, Scotland 1716, Germany and Italy 1717, Denmark 1740, and was introduced into North America by shipping in the year 1735.

The microörganism that causes scarlet fever has not been isolated. Numerous investigators have attempted to discover a specific cause, but none of the bacteria has stood the test of study by later students of the subject. It is quite generally agreed that the cause of most of the secondary complications of scarlet fever is a

streptococcus. Most investigators who have studied this problem have concluded that streptococci are only secondary factors and, while responsible for most of the mortality in scarlet



Streptococcus  
in peritoneal fluid.  
× 1,000 diameters.

fever, are entirely distinct from the real cause of the disease. In scarlet fever the mortality varies in different epidemics from 9 to 15 per cent. Under one year of age the mortality is about 33 per cent.

*Erysipelas* — Erysipelas is an inflam-

matory disease of the skin, caused by a streptococcus discovered by Fehleisen. Erysipelas was described by Hippocrates who had a remarkably clear conception of the disease. Its parasitic origin was first maintained by Henle in 1840. Hueter in 1876 was especially conspicuous in claiming that the disease is caused by a microorganism. It was reserved for Koch in 1880 to settle the question by finding the specific streptococcus in the lymph vessels. Fehleisen made

the same discovery independently of Koch in 1881, isolating and cultivating the streptococcus. An analysis of more than 1,800 cases of erysipelas indicates that age has a decisive influence upon the mortality after the forty-fifth year. The general mortality rate is  $6\frac{1}{2}$  per cent, while in traumatic cases it is  $14\frac{1}{2}$  per cent and in those over seventy years of age 46 per cent.

*Sepsis*—The bacteriology of puerperal sepsis and general septicemia show that streptococcus infection is usually responsible for these conditions. The infectious nature of puerperal sepsis was shown by Dr. Oliver Wendell Holmes in 1843.

#### ANTISTREPTOCOCCUS SERUM THERAPY

When Antistreptococcus Serum was first introduced, the profession was very hopeful that it might cure the many cases of streptococcic infection which had so consistently resisted all attempts of treatment in a high percentage of cases. Experimental work by Weaver and Tunncliff shows that the injection of Antistreptococcus Serum into animals is followed by an increased phagocytic power of the leukocytes of brief duration, and increased opsonic power for

streptococci for a period of about ten days. Weaver advises that if the serum is to be used in a curative way, it should be given early; and if one wishes to obtain a rapid effect, it should be administered intravenously. The benefit from the serum is shown by a prompt fall in the temperature, increase in the opsonic index, reduction of leukocytosis, and by clinical improvement in the patient's condition.

*Scarlet Fever*—The treatment of scarlet fever by injection of Antistreptococcus Serum has been practised for some time. Escherick, von Pirquet, Schick and others believe there is a shortening of the course, reduction of fever, and general improvement in the disease. Some workers have used the serum with the expectation of curing or influencing the fever, believing the disease to be due to streptococci; but most men have used it to combat what they consider a secondary infection. The patients most likely to improve under serum therapy are those who become severely ill after the onset of the disease and the appearance of the eruption.

Baginsky of Berlin was one of the first practitioners to use Antistreptococcus Serum in a large series of carefully studied cases; but the

greatest advocate of Antistreptococcus Serum has been Moser of Vienna. The serum employed by him is obtained from horses which have been immunized against streptococci grown directly from fatal cases of scarlet fever—the bacteria being secured post-mortem from the heart's blood.

Axenow reports (*Jahrbuch für Kinderheilkunde*, 1915, xxxi, No. 2) the use of Moser's serum in 1,335 cases of scarlet fever, and extols serotherapy in the severer cases as the only means known to date which is able to ward off the fatal outcome. It is best given not later than the third or fourth day and the dose should not be fractioned. The serum ought to be reserved for the severer cases and for children more than a year old. According to Axenow, kidney complications are extremely rare in those given serum treatment.

*Septicemia*—The enthusiastic reception of serum therapy for the treatment of septicemia was followed by a period of skepticism; and the medical profession still relegates the treatment in general to the class which may be regarded as promising, but not yet proven. However, as time goes on, the number who employ serum

therapy in this condition, and with a sufficient percentage of success to encourage them in its continuance, is steadily increasing. Therefore, the report of Dr. A. C Burnham (*Annals of Surgery*, May, 1914) is particularly timely and of special importance since it deals with 111 consecutive cases of severe infection, collected from the records of the Presbyterian Hospital, New York City, in which either the course and symptoms were those of septicemia or in which cultures showed the presence of bacteria in the circulating blood. These cases occurred between 1905 and 1913 and represent not the therapy of one physician, but rather the treatment of a group of physicians and surgeons on the various services of a general hospital.

Burnham points out that septicemia with true bacteriemia, though a disease of exceedingly high mortality—especially in the type associated with malignant endocarditis and in terminal infections—is in many cases amenable to treatment. He states that the results were especially favorable when Antistreptococcus Serum was given early. The reports of cases of true bacteriemia were especially favorable and indicate the value of this serum in severe

blood infections. Burnham concludes that Antistreptococcus Serum is of great value, especially during the early stage when its bactericidal powers are most pronounced; and, if given in sufficient doses during the period of invasion, will often change a systemic bacteriemia into a localized infection.

*Locally*—Antistreptococcus Serum has been used to a limited extent as a *local application*, notably in cases of septic endometritis. The uterus is packed with gauze saturated with serum and left for twenty-four hours, being renewed as often as symptoms demand. In a large number of cases thus treated by Dr. William E. Studdiford at Bellevue Hospital, there was a fall of temperature and pulse with prompt subsidence of discharge and restoration to normal condition. Those who have had personal experience are practically unanimous in their belief of the superiority of this over other forms of local treatment.

The serum has been used as a spray for the throat in cases of streptococcic sore throat. Spiess (*Deutsch. med. Wochensch.*, 1912, xxxviii, 207) used it with advantage in the form of a paste as a direct application to the tonsils, and

Sexton (*Archives of Pediatrics*, 1913, xxx, 81) has found it very efficient when applied as a moist dressing to infected wounds. It appears that a more extensive trial in this local manner would be desirable as in many cases the serum would thus be brought into direct contact with the infecting bacteria.

Judging from what occurs in experimental animals, Antistreptococcus Serum should be an efficient prophylactic agent against streptococic infections in man, and its use before certain operations—such as those about the mouth, after which streptococcus infections are liable to occur—seems justifiable.

*Dosage of Serum*—The dosage of this serum as laid down by the foreign investigators should be 200 c.c., followed in twelve to twenty-four hours by one-half this dose. The method employed and recommended by the New York City Department of Health is to inject 200 c.c. for the initial dose in adults, the injection preferably being given intravenously. If given subcutaneously, 100 c.c. are injected in either side of the anterior abdominal wall. The initial dose is followed in twelve to twenty-four hours by 100 c.c. For infants, the initial dose is usually 100

c.c. Dr. Mathias Nicoll of the New York Scarlet Fever Hospital (*American Journal Diseases of Children*, July, 1911) states that the serum given in full doses before the fifth day greatly increases the chance of recovery, even in apparently hopeless cases; that in the large majority the temperature falls by crisis within twenty-four hours, or if by lysis the course of the fever is shortened. The occurrence of complications is less frequent and their gravity diminished. In all severe cases of scarlet fever, the serum should be made use of in full doses and without delay.

Antistreptococcus Serum is bactericidal and consequently must be used early. If its administration is long delayed for the bacteriologic examination, much valuable time may be lost and the opportunity for securing the best results will have passed.

The rapidity with which the serum enters the blood after injection is an important factor in determining its therapeutic effect. *If it is injected directly into a vein its whole effect occurs almost immediately*; if into the muscles it occurs after a few hours, while if beneath the skin the full effect is not reached before two

days. On this account the serum should be administered intravenously, especially in urgent cases.

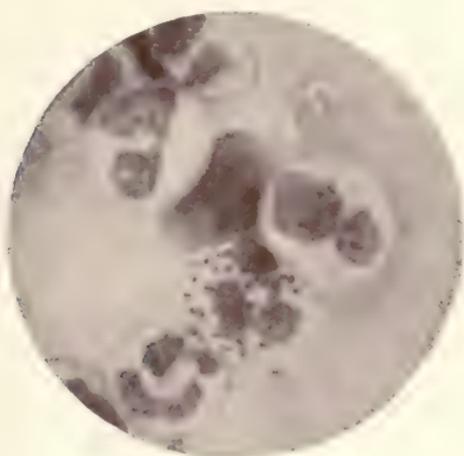
#### ANTIGONOCOCCUS SERUM.

The unfavorable criticism accorded Antigono-coccus Serum has been due to two factors: (1) Improper use of the serum, and (2) small dosage. In the serum of animals immunized against gonococci, Torrey has demonstrated agglutinins, precipitins, and bactericidal and complement fixing bodies. Rogers and Torrey (*The Journal A. M. A.*, 1907, XLIX, 918) first introduced a polyvalent serum prepared by immunizing rams against several strains of gonococci.

*Clinical Reports*—A number of clinicians have reported the successful use of the serum in gonococcus infections of the joints and tendon sheaths, and in epididymitis. In most of the cases reported, the serum has been used subcutaneously. It is generally conceded that the serum has produced no beneficial effects in infections of the mucous membranes. The product was originally marketed in 2 c.c. doses, and all the reports until recently have been on the use of this small dosage; and the results have usually been disappointing. Naturally, good

results cannot be expected from such small doses of any antibacterial serum, since the antibodies are not present in sufficient quantities.

*Indications*—Antigonococcus Serum is recommended in the treatment of complications fol-



Gonococcus in pus cells.  
× 100 diameters.

lowing a primary gonococcus infection; that is, conditions which may be of an acute nature, but which are complications of a prior infection—thus, complications which occur as a result of direct extension of the primary infection into other organs, such as the prostate, bladder, epididymis, testicle and Fallopian tubes; and those due to the entrance of the bacteria into the

circulation, including arthritis and endocarditis. The serum may also be well used in acute urethritis to prevent the spread of the infection into these other organs, but large doses are necessary.

*Dosage*—Never less than 10 c.c. should be given at a dose; and to secure the most satisfactory and at the same time the quickest results the serum is best administered intravenously in doses of 50 to 100 c.c. In malignant cases the initial dose may be 100 to 200 c.c. If the physician prefers not to use the intravenous route, the serum may be injected subcutaneously into the anterior wall of the abdomen—100 c.c. being injected on either side. The doses are usually repeated at intervals of 24 to 48 hours; but, in toxic cases, the serum may be given every 12 to 24 hours. The clinical symptoms must inevitably be the guide for repeating the injections—that is, if the patient responds to the first dose and shows improvement, the second dose may not be required until a day or two later. By using a large initial dose, the infection is more quickly brought under control; fewer doses are necessary; and the expense of the treatment thereby lessened.

*Results*—Dr. B. C. Corbus of Chicago (*The Journal A. M. A.*, May 9, 1914) has reported a series of twenty-four cases treated with Antigonococcus Serum and, as a result of his clinical experience, he recommends at least 36 to 45 c.c. for the dosage. He states: “In the series of cases in which the quantity of the serum given was 36 c.c. or over, the results have been prompt and very encouraging. Invariably when the amount of serum injected was under 20 c.c. the improvement was slow or a relapse occurred.

“My reasons for giving 36 to 45 c.c. of the serum as a sufficient quantity to produce a curative effect are wholly arbitrary and based on my previous experience. In every case in which 36 c.c. or over has been given no treatment was instituted other than prostatic massage and urethral massage over a sound.

“The amount injected should be at least from 36 to 45 c.c., administered intramuscularly, from 12 to 15 c.c. a day, for 3 days. I believe, however, that the intravenous administration, when feasible, would be followed by a more rapid recovery, with a possibility of using less serum.”

The effect of the serum in cases of epididymi-

tis is shown by the almost immediate relief of pain. At times within two or three hours there is considerable amelioration, and patients who have been unable to sleep on account of pain enjoy a refreshing rest. The pain to pressure is also less marked and the acute inflammatory swelling and edema rapidly disappear within 24 to 36 hours.

#### ANTIMENINGOCOCCUS SERUM

*Historic*—Epidemic cerebrospinal meningitis is a comparatively modern disease. Its distinct recognition dates back no further than 1805 when Viesseux in Geneva pointed it out as a separate disease, although there can be little doubt that it existed previously. Symptoms that almost conclusively point to this disease are described in the histories of the great epidemics of Europe from the thirteenth century on.

*Prevalence*—Cerebrospinal meningitis is an acute infectious disease with a characteristic local lesion in the meninges and tissues of the brain and spinal cord. America is peculiarly the home of this disease, and it is difficult in studying the literature to account for this fact.

Cerebrospinal meningitis is most prevalent in the winter and spring, and is primarily a disease of young children—the greater number of cases occurring before twenty years of age. On the whole, it would appear as though children under ten years of age were most susceptible to the disease; for, in the epidemic of 1905 in New York City, 67 per cent of the 2,180 cases occurred in children under ten years of age.

*Mortality*—The average mortality of cerebrospinal meningitis in this country and in Europe, before serum treatment was instituted, ranged between 70 and 90 per cent. Thus, in the epidemic of 1904-5 in New York City, in which there were 6,755 cases, 90 per cent died. In children under five years of age the mortality was 100 per cent.

*Flexner's Work*—Although the etiologic factor in epidemic cerebrospinal meningitis was completely described by Weichselbaum in 1887 as the diplococcus intracellularis meningitidis, no specific remedy was evolved until 1906 when Dr. Simon Flexner, Director of the Rockefeller Institute for Medical Research, perfected Anti-meningococcus Serum. Almost coincidentally, Jochmann of Breslau reported a series of cases

which had been treated by the subcutaneous injection of a serum which he had prepared. Flexner laid a rather more thorough basis for therapy in careful animal experimentation. He produced the typical disease in monkeys by intraspinal inoculation of meningococci, and then saved the animals from death by following the infection with the injection of serum intraspinaly six hours later. The results with the serum produced at the Rockefeller Institute have since proved to be uniformly favorable. The serum was successfully used by Dr. Claude Ker of Edinburgh and Dr. Gardner Robb of Belfast. The *method of intraspinal administration* of the serum, after the removal of cerebrospinal fluid, was the method finally adopted by Flexner as most favorable, and this is the method in current use today.

*Results*—Since the application of serum therapy, the mortality from cerebrospinal meningitis has been reduced from 90 per cent to about 15 per cent. In the Texas epidemic of 1912 the mortality in some of the small towns was as low as 10 per cent.

#### RATIONALE OF SERUM TREATMENT

The present recognized treatment of epidemic

cerebrospinal meningitis is one of the greatest scientific achievements of the twentieth century. The treatment consists of the removal from the spinal canal of the exudate caused by the infection, and of the introduction of a specific antibacterial serum. In all inflammations of the meninges, provision must be made for the relief of the hydrocephalic symptoms resulting from the confinement of the exudate in the meninges—which are bounded on one side by the bony skull and on the other side by the softer brain tissues. As the fluid collects in larger quantities, pressure is thus exerted on the important centers within the brain.

At first the serum was used subcutaneously and intravenously in varying doses which produced the indifferent results. Flexner first proved by experimental tests in the monkey that Antimeningococcus Serum introduced intraspinally offered best results. The subsequent clinical use of the serum in this way helped to definitely establish it as a reliable therapeutic agent of tremendous possibilities. In order to attain good results in cerebrospinal meningitis with the specific Antimeningococcus Serum, the serum must be intro-

duced directly into the subarachnoid space by means of lumbar puncture, so that it will be brought into close contact with the infected area.

A study of the results obtained in some 13,000 cases convinced Flexner that *the serum should be administered intraspinally by the gravity method*, and this is now advocated by most clinicians in this country and abroad. The container illustrated on page 145 has been especially devised for the express purpose of supplying a means for this method of administering the serum.

*Dosage*—The quantity of serum introduced should usually be slightly less than the amount of fluid withdrawn. The dose is usually 5 to 15 c.c. in infants and children, and 30 c.c. or more in adults. The injections of the serum are to be repeated at intervals of 24 hours, and each injection is to be preceded by withdrawal of cerebrospinal fluid. Usually four to six injections of 5 to 15 c.c. each, at intervals of 24 hours, are required for infants and children; and a like number of injections of 30 c.c. each, at the same intervals, are necessary for adults; but as many as 15 or more doses may have to be given. If

relapse occurs, repeat the doses at 24-hour intervals.

#### METHOD OF INTRASPINAL ADMINISTRATION

The technic includes that required for performing a lumbar puncture, inasmuch as the serum must be introduced into the spinal canal *after* the withdrawal of cerebrospinal fluid.

*Preliminary*—The patient is placed on the side (if a child, it may be advisable to first partially etherize), with head bent forward and knees drawn up. The skin in the lumbar region of the back is painted with iodine, or washed with soap and water and followed by alcohol and ether. The operator, whose hands have been sterilized, takes the sterilized needle with its contained stylet in his right hand and introduces the needle through the intervertebral disc between the third and fourth lumbar vertebrae, and a little to one side of the median line; the thumb of the left hand being placed between the spinous processes as a guide.

*Inserting the Needle.*—*The point for inserting the needle* may be conveniently located by placing the index and third fingers of the left hand on the highest points of the iliac crests. The middle finger will then rest on the third

lumbar spine, and the point of election is midway between this spine and the one immediately below it. The needle should be cautiously pushed forward until the slight resistance of the dura is felt; this occurs at a depth of about two centimeters ( $\frac{3}{4}$  inch) in infants, and at 4 to 6 centimeters ( $1\frac{1}{2}$  to 2 inches) in adults. If bony resistance is encountered, withdraw the needle slightly and change the angle of insertion. As soon as the dura has been punctured, the stylet should be withdrawn, and cerebrospinal fluid will begin to flow from the needle.

*Cerebrospinal Fluid*—The fluid is usually cloudy or turbid, and escapes slowly; if there is no flow, or if the flow ceases too soon, the needle may be rotated or its lumen freed by the introduction of the stylet, or the needle may be introduced a trifle further. The fluid should be allowed to flow from the needle into a sterilized test tube, and should be examined bacteriologically to determine the presence of meningococci. However, the serum should be injected immediately without waiting for bacteriologic examination; but a second injection of serum is not to be given until examination of the cerebrospinal fluid shows the presence of the meningococcus.

In infants and young children, about 15 to 20 c.c. of fluid may be withdrawn, and in adults, 40 to 60 c.c.; the fluid being allowed to flow until the cerebrospinal fluid pressure falls to normal: one drop from the needle every 3 to 5 seconds being about normal.

*Blood Pressure Guide.*—In the administration of this serum, the blood pressure method of control, as recommended by Flexner and by the New York City Department of Health, is the safest means of estimating the amount to be given; and if only a small amount of cerebrospinal fluid is obtained, or in cases of a dry puncture, this method is of especial value. It has been noted that the blood pressure falls during the injection of the serum and that the degree of fall may be used as a guide to the quantity of serum that can be safely injected. As a result of observations in many cases, it has been found that a total fall of 20 m.m. of mercury in a person with an initial blood pressure of 110 to 120 m.m. indicates that the further injection of serum should be stopped. The degree of fall in blood pressure that may be safely allowed during the introduction of serum can be fairly well determined by considering a fall of

20 m.m. safe for a blood pressure of 110 m.m. of mercury or over for an adult; and for children the same relative fall may be allowed.

*Adjusting the Apparatus*—After the fluid has been withdrawn, the glass cylinder is attached to the needle *which is left in position*; and the serum, having been gently warmed to body temperature, is allowed to flow into the spinal cavity by gravity. (*Care must be exercised not to heat the serum above 98.6° F., otherwise it may coagulate!*) The adjustment of glass cylinder to needle is effected in the following manner:

Withdraw the soft cotton cord from the rubber tubing (the cord prevents collapse of tubing while in the package); remove one of the rubber caps from the glass cylinder and slip rubber tubing over the exposed end of cylinder. Hold the cylinder vertically and remove rubber cap from upper end of cylinder until serum escapes from metal tip of rubber tubing (thus expelling all air from tubing); then replace the cap and firmly insert the metal tip of rubber tubing into hub of needle. Now remove the rubber cap from upper end of glass cylinder, and adjust the rubber portion of rubber-and-glass union to exposed end of the glass cyl-



Complete outfit for intraspinal administration of  
Antimeningococcus Serum.

inder. (The cotton filter, in glass portion of  
union, prevents any foreign matter from gain-  
ing access to, and contaminating the serum.)  
*From 10 to 25 minutes should be allowed for the*

*serum to be introduced into the spinal canal.* The flow may be increased or decreased by raising or lowering the glass cylinder. *If any difficulty is experienced in starting the flow of serum,* the operator may blow gently in the top of glass tube containing the cotton filter.

The physician is enabled to observe, by means of the short glass tubing near metal tip of rubber tubing, the instant that all of the serum has been introduced; and thus air can be prevented from being forced into the spinal canal.

When the desired amount of serum has been introduced, the needle with the attached glass cylinder is rapidly withdrawn and the puncture wound is sealed with collodion. The patient should be placed in a recumbent posture and, if there is delirium or severe headache, the patient's head should be lowered.

Symptoms of shock or collapse during the injection of the serum are best treated by raising the head of the patient and immediately removing fluid from the spinal canal. If necessary, use artificial respiration and administer stimulants hypodermically.

## Chapter XI

### NORMAL SERUM THERAPY

*Normal serum*, in contrast to antibacterial sera, does not contain any specially induced antibodies but is used solely for its hemostatic property, and is obtained from the blood of animals that have not undergone a process of immunization. Normal horse serum or normal rabbit serum is most frequently used, although normal human serum has been used in a few cases. Human serum is not easily obtainable and, for obvious reasons, horse serum is more satisfactory from a commercial standpoint.

*Composition*—Normal Horse Serum contains properties which increase the coagulability of the blood. These properties are derived probably from the disintegration of blood platelets and leukocytes. The serum differs from whole blood in that it contains no fibrinogen and no formed cellular elements. The hemostatic properties of Normal Horse Serum may be demonstrated *in vitro* by its causing formation of clot in plasma.

*Clinical Use*—Clinical results leave little

doubt that Normal Horse Serum administered subcutaneously or intravenously is a valuable hemostatic in cases of hemorrhage. Also that it may be a valuable prophylactic agent before operation in individuals with a hemorrhagic tendency, but we are as yet ignorant of its mode of action. It has been used fairly extensively and the accumulated experience indicates that there is little, if any, danger of producing intravascular clotting.

*Indications*—Normal Horse Serum is used in the treatment of so-called hemorrhagic diseases including hemophilia, hemophilia neonatorum, purpura and hematuria—diseases in which the tendency to bleed is dependent upon some disturbance of the factors in the coagulation of the blood. Normal Horse Serum is also used for other forms of hemorrhage—epistaxis, metrorrhagia, hemorrhage from wounds and fractures—and, in connection with surgical operations, to prevent postoperative hemorrhage. The long list of diseases with which hemorrhage may be associated justifies the large field in which Normal Horse Serum may be applied.

*Hemophilia* may be defined as a hemorrhagic diathesis, hereditary or otherwise, character-

ized by a predisposition to profuse or uncontrollable hemorrhage which may be spontaneous or induced by an injury. Hemorrhage induced by the slightest wound is the chief factor, while spontaneous hemorrhages are of secondary importance and are often hard to differentiate from certain forms of chronic purpura. In spite of various theories advanced by Sahli, Weil, Nolf and Herry, the cause of hemophilia is still shrouded in mystery; one fact remaining, namely, the non-coagulability of the blood or its delayed coagulation.

*Historic*—Among the first to use serum therapy for hemophilia was Bienwald, who employed it for intractable hemorrhage from the scalp in 1897. A cure resulted. Frey in 1898 successfully treated three cases of hereditary hemophilia by subcutaneous injections of Normal Horse Serum. Welch in 12 cases of hemophilia neonatorum obtained successful results, when previously 17 out of 18 cases treated with calcium, gelatin, or adrenalin had died. Weil has perhaps attained the best work in connection with this form of treatment. In one patient he succeeded in shortening coagulation from 4½ hours to 40 minutes.

## ACTION OF NORMAL SERUM

The sole object of serum therapy in hemorrhagic diseases is to supply the blood with those properties that are lacking to cause coagulation. Normal Horse Serum increases the coagulability of the blood and, when applied locally, exercises a hemostatic action in controlling external hemorrhage. *When injected intravenously, the greatest efficiency of the serum is attained* within a few minutes after its injection; while after its subcutaneous administration, the maximum action of the serum probably does not occur until 12 to 36 hours after its injection.

Although Morawitz and others have shown that on standing a few days, thrombin is converted into an inactive form—metathrombin; nevertheless, laboratory and clinical experiments have demonstrated that the hemostatic power of *Normal Horse Serum that has been kept for two years is still active*. Clinical evidence (Thiesen, *The Journal A. M. A.*, July 18, 1914, and Thiesen and Fromm, *New York Medical Journal*, Oct. 31, 1914) shows that the injection of Normal Horse Serum in hemophilic patients is followed by increased coagulability of the blood.

**DOSAGE AND ADMINISTRATION**

In hemophilia, the usual dosage is 10 to 20 c.c. given intravenously. It is apparently most prompt in its action and most efficacious when given intravenously. Sometimes a single dose suffices to stop the hemorrhage. In cases of continued bleeding, the dose may be repeated at intervals of two to six hours or even longer, depending upon the urgency of the indications. For hemophilia neonatorum and hemorrhage from the umbilical cord, 10 c.c. should be given subcutaneously and repeated three times daily or even every two hours. As a preventive for postoperative hemorrhage, 20 c.c. are administered subcutaneously on the day preceding the operation.

In severe epistaxis, the nares may be plugged with gauze dipped in the serum; and in metrorrhagia, the uterus and vagina are tamponed with sterile gauze saturated in the Normal Horse Serum. For topical application to wounds, sterile gauze saturated with the serum may be applied freely to oozing surfaces.

## Part III

### SERUM DIAGNOSIS

#### Chapter XII

##### COMPLEMENT FIXATION

A detailed account of the immunologic methods of diagnosis would lead us too far and would indeed furnish sufficient material for a special volume. Moreover, the technic employed in serum diagnosis is such that results can only be elicited with any degree of accuracy by skilled laboratory workers. Nevertheless, it may not be out of place to consider here some of the more important methods; for every physician should know the significance, the general facts and the practical application of these methods.

*Nature of Reagents Used*—The principle of complement fixation, discovered in 1901 by Bordet and Gengou (*Annales de l'Institut Pasteur*, 1901, xv, 290), has been utilized both in bacteriologic investigations and in practical diagnosis for the determination in serum of the

presence of specific antibodies. In order to arrive at a clear perception of the phenomena of complement fixation, it is essential that we first have a clear idea of the nature of the substances involved in the reaction. (1) ANTIGEN is a substance which has the power of inducing in the animal body, after one or more inoculations, the formation of antibodies of the amboceptor type. Antigens comprise enzymes, toxins, and protein bodies including bacterial proteins of bacterial vaccines. (2) AN ANTIBODY is one of the constituents of the blood of animals rendered immune by inoculation and exerting a specific antagonistic influence on the substance under whose influence it was formed—that is, the antigen. Antibodies include antitoxins, agglutinins, precipitins, and amboceptors (bacteriolysins, hemolysins, and probably opsonins). (3) COMPLEMENT is a ferment-like body normally present in all sera when freshly drawn from the body, but is very unstable and disappears gradually on standing. Fresh serum may be rendered free of complement or “inactivated” by heating to 56° C. for one-half hour. Complement is the active element of lysis (dissolution of cells or of antigen), but it can act only in con-

junction with the amboceptor, or antibody, which serves as an intermediary for fixing or binding the complement to the cell or antigen on which it acts. (4) HEMOLYTIC AMBOCEPTOR is the lysin antibody of the serum of a rabbit which has been immunized against sheep red cells. (5) As the phenomenon of complement fixation is invisible, RED BLOOD CELLS from the sheep are used as an indicator of the reaction.

*Hemolysis*—In order to demonstrate fixation of complement, the phenomenon of hemolysis is brought into use. Hemolysis consists of the breaking up of the red blood cells with the consequent passing of hemoglobin into solution, the originally opaque fluid becoming transparent. The “hemolytic system” consists of three substances—red blood cell suspension, hemolytic amboceptor and complement; and the presence of all three in definite proportions is necessary for hemolysis.

*Principle Involved*—The reaction in complement fixation depends upon the fact that when a specific quantity of antigen is mixed with the proper volume of its homologous inactivated antiserum, in the presence of a definite amount of complement, all of the complement is firmly

fixed by the interaction of antigen and antibody in such a way that it can no longer be found free in the mixture. If such a mixture is allowed to stand at a suitable temperature for a certain period and then to it is added an emulsion of red cells, together with hemolytic amboceptor, no hemolysis will take place since there is no free complement available to complete the hemolytic system. If, on the other hand, the first mixture contained no antibody for the antigen used, the complement present is not fixed and is free to act—with the aid of the hemolytic amboceptor—upon the red cells, causing dissolution or hemolysis. Thus, the reaction depends upon the fact that neither the antigen alone nor antibody alone can fix complement, but that this fixation is carried out only by the combination of antigen plus antibody.

*Practical Application*—The Bordet-Gengou phenomenon of complement fixation is used in the diagnosis of various infectious diseases, notably gonorrhoea and syphilis; in the differentiation of proteins; in the standardization of antibacterial sera; and in establishing the etiology of infectious diseases. The phenomenon has been extensively used by Wassermann and

Bruck, Neisser and Sachs and others, to demonstrate the presence of immune bodies in various sera. When used for the diagnosis of syphilis, this test is termed the "Wassermann Reaction."

*Essential Factors*—As pointed out by Kolmer, the following factors are essential to the successful carrying out of the complement fixation test: (1) Reliable reagents, particularly a good antigen, must be used; for good results cannot be secured with indifferent reagents, no matter how much care is exercised; (2) There must be an accurate adjustment of the hemolytic system; (3) The observer must possess a thorough working understanding of the underlying principles and the quantitative relations of the various reagents; and (4) He must have a careful, painstaking and accurate habit of pipeting small amounts.

#### TECHNIC OF COMPLEMENT FIXATION TEST

Five substances are required to carry out the test: (1) Immune serum, (2) Antigen, (3) Complement, (4) Hemolytic amboceptor, and (5) Red Cell suspension.

*Immune Serum*—The method of withdrawing

serum depends upon the animal and the purpose of bleeding. In obtaining blood for complement fixation tests on human subjects, blood is most easily obtained from the median basilic vein of the elbow. In the case of a horse, blood is obtained from the jugular vein, while rabbits are usually bled from the carotid artery. The blood is allowed to clot and the clear serum, which forms as the clot shrinks, is obtained by pipetting or pouring, and then is entirely freed from red cells by centrifugalization. Before being used in the test, all immune sera should be inactivated—that is, heated for one-half hour at  $56^{\circ}$  C. to destroy the anticomplementary properties and any natural complement that may be present.

*Antigen*—The method of preparing antigen depends upon the nature of the test to be made, and is described on pages 162 and 164.

*Complement*—According to Noguchi and Bronfenbrenner, fresh serum from the guinea-pig possess unusually active complement. To obtain it, guinea-pigs are bled from the throat into Petri dishes which are left at room temperature until the blood clots—the serum is then drawn off with a pipet. Complement deterior-

ates rapidly if exposed to a warm temperature, but may be preserved for some time by freezing. Complement is usually used in a 10 per cent solution made with physiologic salt solution.

*Red Cells*—Red blood cells from various animals may be used, but the cells must be washed free from serum with physiologic salt solution. In our laboratories, sheep's cells washed six times are used in a 5 per cent suspension. A sheep is bled from the jugular vein into a sterile bottle containing glass beads and, before the blood coagulates, it is thoroughly shaken for the purpose of defibrination. The cells are washed by mixing a small amount of the blood with physiologic salt solution in graduated centrifuge tubes, and the mixture is centrifugalized long enough for the red cells to settle to the bottom of the tubes.

*Hemolytic Amboceptor*—Hemolytic amboceptor is obtained by successive intravenous inoculations of a rabbit with thoroughly washed sheep's red cells—hence the name, Anti-Sheep Amboceptor. Before being used in the test, the hemolytic amboceptor and the antigen must first be standardized by preliminary titrations in or-

der to determine the unit. A unit of hemolytic amboceptor is the smallest amount that gives complete hemolysis of 0.1 c.c. of a 5 per cent suspension of sheep's red cells, in the presence of an excess of complement, after one hour's incubation in a 37° C. water bath. A unit of antigen is the smallest amount which, with two units of hemolytic amboceptor, gives complete fixation of complement.

#### MAKING THE TEST

In carrying out the test, the reagents are mixed in small glass tubes of about 2 c.c. capacity which are placed in suitable racks. Various dilutions of the immune sera are first made. Definite quantities—accurately measured by special pipets—of serum, antigen, and complement, are placed in the series of glass tubes. The mixtures are thoroughly shaken and the racks containing the tubes are placed in a water bath for one-half hour at 37° C. No test is of value unless suitable controls are made. For this purpose, tubes containing known positive serum, tubes containing normal serum, and tubes without any serum but containing an excess of antigen, are run as controls. If the

serum being tested contains specific antibodies, the complement soon becomes used up or fixed so that it no longer remains free; but with a negative serum containing no antibodies, the complement is left free. This is the first step in the process.

At the end of the half-hour incubation period, the tubes are removed from the water bath and definite quantities of hemolytic amboceptor and sheep's red cells are added. The tubes are thoroughly shaken to cause a uniform mixture and are returned to the water bath for one hour. At the end of this time, the tubes are removed from the water bath and the reaction recorded.

#### RECORDING THE TEST

If the complement has remained free (showing that the serum contained no specific antibodies) it acts with the hemolytic amboceptor causing dissolution of the cells, thereby liberating the hemoglobin and producing a clear transparent liquid. This result is called *hemolysis* and constitutes a negative reaction. If the serum contained specific antibodies, the complement will have been fixed by means of the antibodies to the antigen. In the formation of

the antigen-antibody compound, the complement is entirely used up and therefore cannot act upon the red cells. The fluid in the tubes remains opaque but, on standing, the cells gravitate to the bottom of the tubes leaving a clear, colorless supernatant fluid. This phenomenon of disappearance of complement in the mixture of antigen and antibody is now generally called *fixation of complement* and constitutes a positive reaction. Sometimes it is called *deviation of complement* on account of the fact that the complement has been deviated by the combination of antigen and antibody and prevented from participating in the hemolytic process. Thus, it will be seen that the hemolytic system acts simply as an indicator to demonstrate an action otherwise without manifestation.

#### COMPLEMENT FIXATION IN THE DIAGNOSIS OF GONORRHEA

The phenomenon of complement fixation was first applied to the study of gonococcus infection by Mueller and Oppenheim in 1906. The technic developed by Schwartz and McNeil has been widely followed and the value of the test in the diagnosis of secondary gonococcus in-

fections, especially in conditions in which a bacteriologic diagnosis is difficult—notably, in arthritis—has been thoroughly established. The test is performed in the usual way as outlined above. The antigen used consists of a bacterial extract prepared from a 24-hour agar growth, washed off with distilled water and autolyzed. A polyvalent antigen made from as many different strains of the gonococcus as possible, is essential.

*Practical Value*—A positive complement fixation test is indicative of the presence, or recent activity in the body, of a focus of living gonococci. A positive reaction may persist from six to eight weeks after a cure has been effected. Persistently negative results, obtained through a considerable period of time, indicate the probability of a cure. The reaction is seldom positive during the first four to six weeks of an acute anterior or posterior urethritis, in the absence of complications. During the course of an acute or a subacute urethritis, the occurrence of an acute complication—such as prostatitis or epididymitis—is likely to result in a positive fixation test. In women, the reaction is seldom positive until the infection has reached the cer-

vical canal. In the case of children, however, positive reactions have been known to occur in acute and chronic vulvovaginitis, indicating either that the disease is more severe in children, with more antibody formation, or that it may reach the cervical canal.

The administration of Gonococcus Vaccine and Antigococcus Serum is likely to be followed by positive reactions. Just how long the antibodies may persist in the blood after a clinical cure has been effected, it is difficult to state: at least from six to twelve weeks' time should be allowed for them to disappear. Finally, it must be emphasized that the complement fixation test has far more positive than negative value from a clinical standpoint. The reaction is highly specific, but there is a limit to its delicacy, so that a negative reaction in urethritis does not exclude the possibility of gonococcus infection.

#### THE WASSERMANN REACTION IN SYPHILIS

Wassermann, Neisser and Bruck were first to apply the Bordet-Gengou phenomenon to the diagnosis of syphilis. The antigen originally employed, and still preferred by some workers,

consists of a saline extract of liver from a syphilitic fetus. The exact nature of the antigen that produces the antibodies taking part in the Wassermann reaction is unknown. Although a pure lipid cannot stimulate the production of antibodies when used to inoculate an experimental animal, it reacts outside the body with the antibodies in the blood of the syphilitic. The Wassermann reaction is a lipotropic reaction and is not due to the interaction of specific antigen and antibody. An extract of heart, liver or kidney in alcohol may be used as antigen, and some serologists recommend the addition of cholesterin to the alcoholic extract. A safe and stable antigen is Noguchi's acetone insoluble fraction of beef-heart, liver or kidney.

*Practical Value*—Though biologically non-specific, the Wassermann reaction is clinically specific, except perhaps in cases of leprosy, yaws, sleeping sickness and scarlet fever. A positive reaction may be obtained in any stage of syphilis but is most apt to occur in the secondary stage. A negative reaction at any stage of the disease does not exclude the possibility of syphilis. Antiluetic treatment, especially mercury, frequently results in the reaction be-

coming negative though the disease may still be active. If the Wassermann reaction is persistently negative for two years, after cessation of treatment—tests being made at intervals of three months—it is fairly certain that a cure has been effected.

## Chapter XIII

### OPSONIC INDEX

The frequent mention of the term "opsonic index" in the literature makes it imperative that the physician have a general idea of the technic and significance of the reaction. The opsonic content of a given serum is estimated by comparison with normal serum. By the opsonic index is meant the ratio of the average number of bacteria per leukocyte taken up in the presence of a given serum, to the average number of bacteria taken up in the presence of normal serum.

*Historic*—Metchnikoff discovered that certain leukocytes play a most important part in the process of immunity as phagocytes, by their property of taking into themselves and destroying pathogenic bacteria. Wright and Douglas showed definitely that phagocytosis of bacteria in serum depends upon the presence in the serum of a special substance which acts on the bacteria and sensitizes or prepares them for the leukocytes. They called this substance *opsonin*.

Opsonins exist in the tissue fluids and are substances which are capable of rendering bacteria more susceptible to phagocytosis.

#### THE TECHNIC OF THE OPSONIC INDEX

The reagents taking part in the opsonic reaction are: (1) The serum to be tested; (2) Normal serum which is used as a control; (3) Leukocytic suspension, and (4) The bacterial suspension.

*Leukocytic Suspension*—If human leukocytes are used, they may be obtained by puncturing the lobe of the ear or the tip of the finger with a lancet, and allowing the blood to flow into a solution of one per cent sodium citrate and 0.85 per cent sodium chloride solution. The citrate solution keeps the blood from clotting until the corpuscles are separated from the citrate solution by centrifugalization. Animal leukocytes may be obtained from the guinea-pig or rabbit by injecting the animal with a solution of peptone and collecting the peritoneal exudate eighteen hours later. The leukocytes from whatever source are washed three times with 0.85 per cent salt solution by centrifugalization. After the third centrifugalization, the supernatant

fluid is decanted and a sufficient amount of fresh saline solution is added to make a moderately opaque solution. The suspension is now ready to be used.

*Bacterial Suspension*—The bacteria are grown upon a suitable solid medium and, at the height of their growth, are washed off with a sufficient amount of 0.85 per cent sodium chloride solution to make a moderately opaque emulsion.

#### CARRYING OUT THE TEST

Into special glass tubes are placed, by means of pipets, definite quantities of the serum to be tested and the bacterial suspension. Into other tubes are placed definite quantities of normal serum and the bacterial suspension. The tubes are then incubated for one hour in a water bath. This is to enable the opsonins, in the serum being tested, to prepare or sensitize the bacteria in such a way that they will later be more readily taken up by the leukocytes. At the end of the hour, definite quantities of the leukocytic suspension are added to all of the tubes, which are then returned to the water bath for one-half hour. During this incubation, the

prepared or sensitized bacteria are ingested by the leukocytes.

At the end of the second incubation, the tubes are removed from the water bath, the supernatant fluid decanted and, by means of a sterile platinum loop, a quantity of the sediment consisting of bacteria and leukocytes is removed from each of the tubes which contained the serum to be tested, as well as from the tubes containing the control normal serum; and smears from the sediments are made on microscopic slides. These smears are fixed and stained in the usual way and are then examined under the microscope, and the bacteria in 100 polymorphonuclear leukocytes are counted in each of the stained smears. The average number of bacteria taken up per leukocyte from the serum being tested, divided by the average number of bacteria per leukocyte from the normal serum is the "opsonic index."

#### PRACTICAL VALUE OF THE OPSONIC INDEX

Little of the diagnostic value which was expected of the opsonic test has been realized. An immense amount of investigation has revealed the fact that the opsonic index cannot be ob-

tained accurately enough in single tests to be an accurate guide for use in diagnosis or treatment; and further, that the opsonic content is not a safe guide for the measure of the total antibodies in the blood. According to Wright and Bullock, the opsonic index in normal individuals varies from 0.8 to 1.2. The deviation of the index beyond these limits would indicate that the patient was or had been infected with the microörganism to which the variation in the index existed. A low opsonic content, according to Wright, denotes a lowered resistance and a high opsonic content an increased resistance of the individual to infection. The interest in the subject of opsonins is largely due to the investigations and influence of Wright, who originated the idea of estimating the changes in the opsonic power of the blood for the purpose of guiding the use of vaccines in the treatment of bacterial infections.

*The opsonic index has not been found of much practical value* for two reasons: (1) Because the technic of the test is not only time-consuming but subject to error, so that considerable practice is necessary to obtain reliable results. (2) Variations which are great enough to

be well beyond the range of error are, as a rule, accompanied by other changes which constitute a more reliable means of diagnosis. The variation in the counts is much greater than most examiners believe. North has collected a series of tests, carried out in nearly all the important laboratories in the Eastern United States that are working upon opsonins. The results recorded prove absolutely that, while an average counting error of only about ten per cent is present, there may be an exceptional error of at least 100 per cent; and one of at least 20 per cent may be expected once in about every ten determinations, even by experienced workers. Most value was placed by Wright upon the opsonic index as a guide to the size and frequency of doses of bacterial vaccines in the treatment of disease. As a routine measure, however, the opsonic index has fallen into disuse, and vaccine therapy is being largely guided by the clinical evidences of reaction and the condition of the patient.

## Part IV

# VACCINES IN THE PROPHYLAXIS OF DISEASE

### Chapter XIV

#### PROPHYLACTIC VACCINES

##### SMALLPOX

Vaccines usually employed in the practice of medicine may be divided into three classes: (1) attenuated vaccines (viruses), (2) killed bacterial vaccines of Wright, and (3) pollen vaccine. An *attenuated vaccine* is one in which the virulence has been decreased in some manner, usually by exposure to temperatures unfavorable to the growth of the microörganism or by passage through animals. For example, the virus of rabies was attenuated by passing it through a series of fifty rabbits which rendered the virus of increased virulence for the rabbit but of decreased virulence for man. *Bacterial vaccines* are usually suspensions in physiologic

salt solution of killed pathogenic bacteria—that is, bacteria which are capable of producing disease. *Pollen vaccine* is an extract of the pollen of various flowering plants, grasses and weeds.

The therapeutic action of vaccines consists in the stimulation of the tissue-cells of a patient. This stimulation arouses the tissue-cells to the production of various antibodies, as a result of which the patient is protected against the disease. This type of immunity is termed “active” and may last for a number of years.

The present widespread use of bacterial vaccines dates from the demonstration by Wright and Douglas of the presence of opsonins in sera, and the relation of opsonins to phagocytosis in health and disease as influenced by the administration of bacterial vaccines. By determining the opsonin content of a serum, they were able in many cases to establish the correct dosage of the vaccine and the frequency of its administration.

#### PROPHYLACTIC VACCINATION

The efficacy of inoculation by vaccines, in the prophylactic immunization against certain diseases, may be accepted as established clinically

as well as supported by serologic and animal experiments. The science of immunology dates back scarcely thirty years. Many primitive people attempted to immunize themselves in a crude way, but with methods now recognized as essentially sound. Thus, South African tribes attempted to protect themselves against snake bites by using a mixture of snake venom and gum. The Moors immunized cattle to pleuropneumonia by placing some of the virus under the skin of the animal.

Inoculation against smallpox, used from time immemorial, and inoculation with cowpox introduced by Jenner in 1798 are examples of the first practical use of specific methods in the history of immunology. Jenner's demonstration that a mild form of a disease protects against the severe form, gradually influenced Pasteur who expanded the fact into a general principle. Practically all of Pasteur's work in immunity that bore practical fruit, such as vaccinations against chicken cholera, anthrax and rabies, is based on this guiding principle. It is, indeed, surprising that these phenomena of prophylactic protection, discovered by Jenner in smallpox and developed by Pasteur in rabies, did not

find more general application to the diseases of man. But unfortunately it has not been possible to materially extend the application of this principle, and all important advances have since been made with other means of active immunization.

It was shown by Salmon and Smith in 1886 and by Chamberland and Roux that it was not necessary to introduce living microorganisms in order to produce immunity; and further, that the same result could be obtained by injecting bacteria killed by heat. Vaccination by the use of cultures killed by heat or antiseptics was introduced by Kolle in 1896. In the same year, Wright introduced the use of killed cultures for immunization against typhoid fever, and this method of prophylactic immunization has also been successfully applied to cholera, plague, meningitis, and whooping-cough.

#### SMALLPOX

*Historic*—Smallpox has been known since very early times, particularly in China; and, while there is every reason to believe that it was present in the various countries, the older writers do not give very clear descriptions of it. Smallpox is supposed to have originated in

Africa in prehistoric times. The first historic reference to the disease is an account of an epidemic which developed in the Abyssinian Army besieging Mecca in the year 571. From Mecca it spread through Asia and Europe. Procopius in his history of the Eastern Empire describes smallpox as present in epidemic form in Constantinople in 581, and Gregory of Tours records its presence in Southern France in the same year.

About the first century, however, there can be little doubt of the presence of the disease and numerous widespread and severe epidemics have been reported. The first accurate description is perhaps that of Isaac, but the best of the early descriptions is that of Rhazes who lived in Bagdad about 900. The disease was at first confused with measles, from which it was distinguished by Avicenna; and Sydenham finally gave such a description as to lead to the separation of the two diseases. The disease was probably imported from the Old Country to America early in the sixteenth century, and there were numerous epidemics which exterminated many Indian tribes and reduced others to a handful of individuals.

One thing which is often overlooked in the history of smallpox is the fact that, in prevaccination days, every one had the disease; and, at that time, it was a disease of childhood—the adult population consisting of those individuals who had survived the attack. From the descriptions of writers of that period, almost every one was more or less pock marked and the disease was regarded as a disagreeable necessity, much in the light that we now regard measles. By the year 1600 smallpox had assumed epidemic form throughout Europe and, in the following two hundred years, it continued its ravages unchecked.

*Prevalence*—In England, smallpox was always present and but one person in twenty-five escaped an attack of the disease. From 1761 to 1800 there died in the city of London an average of 2,037 persons yearly from smallpox. Welch and Schamberg estimate that in the one hundred years from 1700 to 1800, an average of 600,000 persons died yearly from smallpox throughout the world.

Statistics show that smallpox has been unusually prevalent in the United States during the past fifteen years, the epidemic of 1901-2-3

causing 4,658 deaths. In 1902 there were reported 54,014 cases with 2,083 deaths. In 1912 there were 22,076 cases of smallpox with 235 deaths officially recorded. It is estimated that ten million people in this country are unvaccinated, and sufficient foci remain to maintain smallpox in epidemic proportions as long as the public cares to tolerate it.

Before the introduction of vaccination, smallpox had become a permanent disease which never entirely ceased in any one year and every third or fifth year became a great epidemic. In non-epidemic years one-tenth of all mortality was from smallpox: in epidemic years one-half. Countless mortals were maimed by loss of sight. It is not uncommon to see in some cities in the Far East six or eight people totally blind being led by a blind leader, each with his hand on the other's shoulder. Of newborn children one-third died of smallpox before their first year of life, while one-half died before their fifth year of life.

Smallpox is highly infectious and no immunity is given by race, sex, or season. Notwithstanding this, so great is the protection given by vaccination and revaccination that a large ma-

majority of physicians have never seen a case of smallpox; and, in civilized lands, we rarely see an individual bearing scars produced by the disease.

*Mortality*—Smallpox is fatal to a very large proportion of those whom it attacks. It kills from 30 to 40 per cent of its victims. In the second, sixth, eleventh and twelfth centuries, the disease ravaged Europe exacting a death toll of over 40 to 70 per cent among primitive races, reaching its zenith in the eighteenth century. At this time, 10 per cent of the total mortality in England was due to smallpox and one person in every five was horribly scarred.

### RESULTS OF VACCINATION

Probably at no time in the world's history has the efficiency of smallpox vaccination been so conclusively demonstrated as in the Philippine Islands since American occupancy. Under Spanish rule, it was necessary each year during the dry season to erect in Manila a large temporary hospital to which the many hundreds of victims of smallpox could be taken—and the great majority of them died. Since 1907 when systematic vaccination was completed in the six

provinces near Manila, which have an approximate population of one million and which from time immemorial had an annual average mortality from smallpox of 6,000 people, not one person who had been successfully vaccinated has died of smallpox and only a few scattering cases of the disease have occurred.

Cuba, with compulsory vaccination laws, has not registered a case of smallpox since 1902. Since the compulsory vaccination law went into effect in Germany in 1874 there have been no epidemics from the disease in the Empire.

#### DISCOVERY OF VACCINATION

Among preventive measures, prior to the discovery of vaccination, inoculation with the disease deserves brief mention. Among the Turks it had long been practised and it was introduced into England in 1721 by Lady Mary Wortley Montagu, who returned in that year from a period of residence in Constantinople. The advantages of inoculation were that one could by this means have the disease when young; when in good health; at a favorable time of the year, and often in a mild form. Among the educated, many availed themselves of this practice; but

it never became popular among the masses, as death frequently followed the inoculation. In the same year (1721) Dr. Zabdiel Boylston, of Boston, introduced inoculation in America. During this year an epidemic of smallpox was present in Boston. There was much opposition to inoculation and the practice ceased on the discovery of vaccination.

Prior to this discovery, it had long been known that an attack of cowpox conferred immunity to smallpox. This fact had been observed by those engaged in dairying and the care of cattle in various parts of the world. Dr. Edward Jenner who lived in Sodbury, England, grasped the significance of this fact and on May 14, 1796, he vaccinated his first case, James Phipps, aged eight years, using serum taken from a cowpox vesicle on the hand of a dairymaid, Sarah Nelmes; and on July first, he proved the immunity of the boy to smallpox by his failure in repeated attempts to give him smallpox, either by inoculation or by exposure to the disease. The experiment was repeated many times in other subjects; and finally, in 1798, Jenner published an account of his work: "An inquiry into the causes and effects of

variolae vaccinae (cowpox).” News of the discovery of vaccination spread rapidly to America, but the difficulty of conveying the Vaccine Virus without loss of potency delayed the first successful vaccination in the United States until July 8, 1800, when Dr. Benjamin Waterhouse, Professor of Medicine in Harvard College, successfully vaccinated his son—a boy about five years of age.

*Preparation of Virus*—By the law of July 1, 1902, Vaccine Virus sold in interstate traffic in the United States must come from a licensed manufacturer. These licenses are issued by the Secretary of the Treasury only after a careful inspection of the plant, personnel, and product by a competent government officer. In accordance with an additional regulation issued by the Secretary of the Treasury March 13, 1906, each lot of Vaccine Virus must be examined fully by modern bacteriologic methods to determine the absence of pathogenic microorganisms.

*Tests*—The following tests are made in our laboratories on all Vaccine Virus in order to insure its safety and activity: (1) Green virus as harvested—before “aging”—is subjected to

careful bacteriologic study. (2) In order to establish the potency and purity of the finished product, the backs of white rabbits are shaved and Vaccine Virus rubbed on the shaved areas without scarification. Active virus will grow and cause characteristic vesicles in 3 or 4 days and the animals recover without serious consequences. (3) The purity and safety of the finished product are further established by bacteriologic study and injections of the Glycerinated Vaccine Virus into guinea-pigs and white mice.

*Deterioration of Virus*—Vaccine Virus rapidly deteriorates unless kept cold—below 50° F.—and there is no way of preventing it from becoming inactive if exposed for any length of time to higher temperatures. Careful experiments show that Vaccine Virus kept at 98° F. for three days is killed: vaccine kept at 70° F. for one week becomes inactive: vaccine kept at 50° F. (ordinary refrigerator temperature) for three to six months remains active; while *vaccine kept at 10° F. for four years is still active.*

Hence, the important factor is the temperature at which Vaccine Virus is kept and not the age of the virus. Therefore, the expiration

date stamped on the packages is not a reliable guide for judging the activity of the vaccine, for unless it is kept at a low temperature the virus soon becomes inactive and will not produce "takes."

The lesson which these experiments teach is: (1) Vaccine Virus should be kept in a refrigerator at a low temperature (about 40° F.) until used. (2) The practitioner must not expect to obtain "takes" if he uses Vaccine Virus that has not been kept at low temperatures.

#### TECHNIC OF VACCINATION

Trivial and simple as the operation of vaccination appears, it is nevertheless a surgical procedure and one requiring skill and special knowledge to secure the most successful and satisfactory results. Moreover, the after-care of the wound is exceedingly important.

The arm, at the insertion of the deltoid muscle, is the safest site for vaccination, since it is more easily kept clean than the leg, especially in infants. In female children, if the leg be chosen in order to avoid a scar upon the arm, special care must be taken to keep the wound clean.

The hands of the operator, the instrument

used, and the site of vaccination should be clean. In preparing the site of inoculation, *use soap and water* and dry with a clean towel. Ether or alcohol may be used, if allowed to evaporate before proceeding with the operation; otherwise the antiseptic may easily destroy the life of the virus. *A single linear scratch about  $\frac{1}{8}$  of an inch long* should be made with a sterile needle; the scratch should not penetrate the subcutaneous tissue,



Single linear scratch about  $\frac{1}{8}$  inch long, extending down to the corium but not deep enough to cause bleeding; ready to be inoculated with Vaccine Virus.

for, if bleeding occurs, virus rubbed into such an incised area will be washed away by the blood. Small scratches have the advantage of healing rapidly and of presenting less danger of secondary infections. *Avoid scarifications or cross-scratching*, as this method produces an abraded surface which is soon covered by a crust of serum and blood, leaving a central irritated wound which invites infection.

With the ivory point or wooden stick rub the virus gently but thoroughly into the scratch, re-

membering that it requires time to properly perform this portion of the operation. In general, the less the skin is irritated the less is the danger of complications. Rubbing in of the virus is very important, and with skilled vaccinators and good virus, every vaccination in a primary subject will take; while with unskilled vaccinators there are usually negative results, due generally to insufficient rubbing in of the virus, or to deep scratches causing bleeding which washes out the virus, or to scratches which are too superficial. After the virus has been applied and carefully rubbed in, the serum on the vaccinated area should be allowed to become thoroughly dry; the length of time which this takes will vary from fifteen minutes to one-half hour.

#### AFTER-CARE

After performing a vaccination, the physician should keep clearly in mind three important points: (1) Usually no dressing is necessary, but great care must be taken to keep the vaccinated arm or leg clean and to protect the vaccinated surface from dirty clothing and from infection by scratching or rubbing. For this purpose an oblong piece of dry sterile gauze of two

or three thicknesses may be loosely applied and retained by two strips of adhesive plaster, one applied around the arm well above and the other well below the vaccination. The gauze should be sufficiently large (2 by 3 inches) to prevent the adhesive strips from irritating the vaccinated area. The gauze protects the wound from external infection, and, where this method is followed, secondary infections practically never occur. (2) No protective dressing should be allowed to remain on the vaccinated area more than twenty-four hours at a time. The use of pads, plasters and shields of any sort is usually to be condemned because, by retaining heat and moisture, they cause softening and breaking down—in other words, they act as a poultice. (3) Vaccination is a surgical procedure and deserves the personal attention of the vaccinating physician on the third, seventh and ninth days at least.

Bathing need not be omitted, nor any of the ordinary occupations; but any unnecessarily excessive use of the vaccinated arm or leg should be guarded against, as this increases the congestion, inflammation, and the chances of infection.

The primary wound soon heals, and no reaction occurs for three or four days; by the seventh day, the vesicle is usually full size; about the ninth or tenth day, the reaction begins to subside; by the twelfth day, the vesicle rapidly dries, leaving a brown, wrinkled scab which finally drops off. A normal scab forms the best protection and should not be removed. If infection of the wound occurs, it should be thoroughly cleansed, the scab being removed if necessary, and a wet dressing of warm 1 to 3,000 bichloride of mercury solution, frequently changed, should be applied.



Typical vaccination produced by single linear scratch about  $\frac{1}{8}$  inch long, with Glycerinated Vaccine Virus. Ten days after vaccination.

#### DANGERS

The alleged danger from vaccination has been greatly magnified by antivaccinationists. The only danger lies in the fact that vaccination produces a wound, which is subject to the complications of any wound. Even a pin prick or a scratch may cause serious results. Most of the

infections after vaccination occur in those in whom the regard for cleanliness is slight, and who neglect to properly protect the wound. In recent years, owing to the improved quality of the Vaccine Virus, the introduction of aseptic methods, and better after-care, serious complications are very rare. In any case, the danger connected with vaccination is infinitesimal when compared with the benefit conferred.

#### REVACCINATION

After a varying number of years, usually five or more, the immunity conferred by the primary vaccination is partially or, less often, completely lost. Every person should, therefore, be revaccinated one or more times. A good rule is to vaccinate in infancy, again upon entering school, and thereafter at intervals of five years until adult life is reached. If smallpox appears in a community, all the inhabitants should at once be vaccinated except those who have been successfully vaccinated within one year.

It should be remembered and taught by physicians that systematic and successful revaccination is just as important for the protection from smallpox as is a successful first vaccination.

## Chapter XV

### RABIES

*Historic*—Rabies has been known for more than 2,300 years, the earliest reference to the disease being that of Aristotle in the fourth century B.C. Celsus in the first century A.D. was the first to give in writing a detailed description of human rabies. Rabies is a rapidly fatal, highly acute specific disease, to which all warm-blooded animals are susceptible. It is always communicated through a wound, usually made by the teeth, the infective matter being the saliva which contains the virus.

*Prevalence*—Rabies occurs in almost every part of the world, Australia being the only country known to be exempt, owing to the rigidly enforced quarantine. In France, Belgium, Hungary and Russia, the disease is widespread. England, because of quarantine and periodic muzzling of dogs, is now reported free from the disease. Rabies occurs in practically every part of the United States. In 1911, Stimson stated that it had been reported in all but six states and there were 1,381 infected localities.

*Animals Affected*—Dogs are most frequently affected with rabies and to them we owe the perpetuation of the disease; they are usually responsible for the transmission of the disease to human beings. Rabies also occurs among cattle, wolves, cats and other animals, and may be transmitted by them to man.

#### NATURE OF THE DISEASE

Rabies is transmitted to human beings through inoculation with virus from infected animals, usually dogs. The saliva of the animal is the infecting medium which conveys the virus. The disease may be transmitted by the deposit of saliva containing the virus on abraded surfaces, as by licking. In all cases, a wound or an abraded surface of the skin is necessary for the absorption of the virus. It cannot pass through the healthy skin.

Following the bites of a rabid animal, no symptoms apart from the wound are noted for a variable length of time, depending upon the severity of the bites, location of the wound and the species of animal inflicting the bites. A bite on the head or face is usually followed by symptoms of the disease within a shorter period than a wound on the hand or foot.

The period of time that elapses between the bite by the animal and the development of symptoms in the individual is known as the period of incubation. This varies from ten days to six months or longer. The majority of cases occur before the end of the third month, the average time being about 72 days.

#### SYMPTOMS IN THE DOG

Rabies presents at least two clinical types: these are the excited, and the paralytic. It is important that the early symptoms of rabies in the dog be recognized; for the bite of a dog may communicate the disease three or five days prior to the development of symptoms in the dog. At this stage, the animal may be playful and affectionate to an unusual degree; he desires to be recognized and petted. Later, there is a marked change in the voice to a hoarse howl, followed by an unequal series of barks, lower in pitch than is normal. The rabid dog becomes restless, lying down and getting up again repeatedly. He is easily startled, growls and barks on slight provocation.

In the *excited type*, the dog may suddenly leave home, wandering off for many miles, to

return in a day or two, emaciated, wounded, and utterly changed. During the period of running mad, he may have bitten many persons and animals. He does not fight other dogs but bites them and passes on. The dog looks sick and takes no interest in his surroundings. It is the rule that dogs in this condition have no appetite for their accustomed food and frequently swallow indigestible objects. Swallowing is difficult and, later in the disease, impossible. Convulsions now appear, and the dog may die in one. More frequently a paralytic stage supervenes: the animal drags himself to a secluded spot; the hind legs become paralyzed first, giving the impression that the spine is injured. Saliva drools from the mouth and the dog becomes much emaciated.

The *paralytic form*, ordinarily spoken of as "dumb rabies", is quite frequent among dogs and offers peculiar danger to man. These are the cases where the owner or bystander endeavors to remove an imaginary bone from the throat and becomes bitten. Spasms of deglutition and paralysis of the throat muscles strongly suggest an obstruction in the throat.

It is a mistake to suppose that rabid dogs have

any fear of water. They are intensely thirsty and desire to drink, but when the paralytic condition affects the throat muscles they are unable to swallow. They are so far from having a fear of water that they sometimes swim rivers while in the excited stage, as observed in ancient and modern times. The term hydrophobia—meaning “fear of water”—is a misnomer, and should be discarded.

#### THE CAUSE OF RABIES

At the present time, the belief is growing that the cause of rabies is a parasitic protozoan discovered by Negri and generally known as the “Negri body.” This was the opinion of Negri from the first. His discovery has been amply confirmed, and most observers agree with his interpretation of the nature of the bodies as well as their significance. Negri has traced a developmental cycle for the parasite, as have Williams and Lowden and Noguchi who have classified it with the protozoa.

The fact that the disease is transmitted through bites of rabid animals—not only of dogs, but of other animals as well—led to the discovery that the causative agent is actually

present in the saliva. Subsequently, it was found that this causative agent, or rabies virus, would be destroyed by heating the saliva, by adding certain chemicals, or by exposing the saliva to sunlight. It was further shown that it is possible to filter out the virus by forcing the saliva through a very fine porcelain filter.

The presence of the virus in its purest form can be demonstrated in the substance of the spinal cord and brain. It is also present in the saliva and salivary glands; and frequently in the milk and mammary glands, and in the lachrymal secretion and glands. Hence, in performing an autopsy upon a rabid animal, care must be exercised not to come in contact with the saliva, brain, spinal cord, or other secretions and tissues which contain the virus; especially when the person has wounds, cuts, or open sores through which the virus may gain entrance.

#### CARE OF ANIMAL

If the animal is dead, its head and about four inches of the neck should be severed from the body and sent to a State, Municipal or other diagnostic laboratory for examination. If the animal is alive, every possible effort should be

made to keep the animal securely confined and under observation for at least two to six weeks, or longer if possible. When an animal is killed in the early stages of the disease, the changes sought for in the brain as indicative of rabies are likely to be entirely absent; and if these changes are not found in an animal killed early in the course of the disease, it does not indicate that the animal did not have rabies. The saliva may have contained the virus at the time of the biting, and the person bitten may be dangerously infected with the disease; for the saliva may contain the virus several days before the animal shows symptoms of the disease.

Hence, rabies may result from the bite of an animal apparently normal at the time of inflicting the wound. Therefore, any animal suspected of rabies should be securely confined and kept under observation; *but antirabic treatment for the bitten individual should be started at once*. On account of the long period of time sometimes necessary for the positive diagnosis to be made in the animal, the disease may have gained an incurable headway; therefore, in suspicious cases, it is often advisable that the treatment be started without waiting for diagnosis,

since *it is important that the treatment of the bitten individual be begun within one week of the bite, if possible.*

#### CARE OF BITTEN INDIVIDUAL

*The Wound*—All wounds should be cauterized as soon as possible—it is never too late to derive some benefit from cauterizing. Thorough cleansing with antiseptic solutions should be followed by the application of undiluted formalin or nitric acid; and an aseptic dressing may then be applied. Whenever there is any reason to suspect that the animal may have rabies, then, in addition to the cauterization and dressing of the wound, arrangements should be made at once for the administration of Rabies Vaccine in the form of preventive treatment prepared after the method of Pasteur.

*The Patient*—The bowels should be kept freely open during the course of treatment, and the drinking of tea, coffee, and alcoholic beverages allowed but sparingly. While taking the antirabic treatment, patients are ordinarily able to attend to their work. Exposure to cold, especially excessive bathing, should be avoided during the course of treatment. Some local

soreness, together with erythema about the site of the injection, may occur. If these signs of reaction are marked, the application of a wet dressing of aluminum acetate solution will be found useful. Slight malaise may also be felt. The producing laboratories should be notified by telegraph of any unusual symptoms.

#### RABIES VACCINE.

*Indications*—Rabies Vaccine is used for the *preventive treatment* of rabies during the incubation period. After symptoms of the disease are fully developed, antirabic treatment is of absolutely no value. A cure for rabies is as yet undiscovered, but the Pasteur treatment is effective in preventing the development of the disease in persons bitten by rabid animals.

*Dosage*—The antirabic treatment consists of the injection of 25 doses of Rabies Vaccine, prepared after the method of Pasteur; the injections being given daily for 21 successive days.

*Method of Administration*—After painting the skin with iodine, the injections are given into the subcutaneous tissues of the anterior abdominal wall or of the interscapular region. The entire amount in each vial should be administered at a single injection. Each subsequent in-

jection should be made in a widely distant area of tissue, and with a freshly sterilized syringe and needle, using vaccine in vial next in order numerically. No after-treatment of the site of injection is required.

*Prognosis*—The outlook is most favorably influenced by the Pasteur treatment. At the Paris Institute, up to January, 1904, there had been treated 17,719 cases of all descriptions with 117 deaths, making a mortality of 0.42 per cent. As in other methods of vaccination, immunity is produced only after a certain lapse of time; and, in cases of short incubation or of late commencement of the treatment, the disease may manifest itself before the effect of vaccine has been procured. The work of Krauss and Kreis-*sel* throws much light on the production of immunity by the Pasteur treatment and emphasizes the importance of beginning treatment promptly. These authors find that the serum of healthy individuals as a rule does not contain any protective property against the virus of rabies, nor is any found immediately after the completion of antirabic treatment; but twenty-two days later, marked antirabic power is present and is retained for a long time.

*How to Secure Treatment*—Because of the perishable nature of Rabies Vaccine, the product cannot be kept in stock by druggists; and requests for antirabic treatment must be telegraphed direct to the producing laboratories, where freshly prepared vaccine is kept in constant readiness. *Such requests should state the age of patient; date, severity and location of bite; and full name and address of physician to whom treatment is to be sent.*

Until recently it has been necessary to go to special institutions maintained for the purpose of giving antirabic treatment. This has practically made it impossible for the physician to avail himself of this treatment for his patients. During the last few years, however, it has been clearly demonstrated that it is possible to supply this treatment in such form as to admit of its use by any physician, irrespective of previous experience in administering the treatment, and without removing the patient from his surroundings. The ability of the family physician to administer this treatment in the patient's own home is heartily welcomed by the patient.

## VACCINES IN PROPHYLAXIS OF DISEASE 201

*Plan of Treatment*—The following plan of Pasteur antirabic treatment is employed:

- Dose No. 1—Immediately upon arrival of vaccine on first day of treatment.
- Dose No. 2—Four hours after first injection on first day of treatment.
- Dose No. 3—Four hours after second injection on first day of treatment.
- Dose No. 4—10 A.M. on second day of treatment.
- Dose No. 5— 4 P.M. on second day of treatment.
- Dose No. 6—10 A.M. on third day of treatment.
- Dose No. 7— 4 P.M. on third day of treatment.
- Dose No. 8—About 10 A.M. on 4th day of treatment.
- Dose No. 9—About 10 A.M. on 5th day of treatment.
- Dose No. 10—About 10 A.M. on 6th day of treatment.
- Dose No. 11—About 10 A.M. on 7th day of treatment.
- Dose No. 12—About 10 A.M. on 8th day of treatment.
- Dose No. 13—About 10 A.M. on 9th day of treatment.
- Dose No. 14—About 10 A.M. on 10th day of treatment.
- Dose No. 15—About 10 A.M. on 11th day of treatment.
- Dose No. 16—About 10 A.M. on 12th day of treatment.
- Dose No. 17—About 10 A.M. on 13th day of treatment.
- Dose No. 18—About 10 A.M. on 14th day of treatment.
- Dose No. 19—About 10 A.M. on 15th day of treatment.
- Dose No. 20—About 10 A.M. on 16th day of treatment.
- Dose No. 21—About 10 A.M. on 17th day of treatment.
- Dose No. 22—About 10 A.M. on 18th day of treatment.
- Dose No. 23—About 10 A.M. on 19th day of treatment.
- Dose No. 24—About 10 A.M. on 20th day of treatment.
- Dose No. 25—About 10 A.M. on 21st day of treatment

## Chapter XVI

### TYPHOID FEVER

*Prevalence*—Typhoid fever is one of the most widespread of the infectious diseases. It prevails more or less in all countries. It occurs in the tropics and in far northern and southern latitudes; at sea levels and in the mountains; in the city and in the country; and practically wherever man may go and where local conditions do not prevent the dissemination of the disease. The typhoid bacillus has about the same limits of latitude and longitude as man himself, and no common race is known to be immune from the disease. In the United States there are comparatively few communities of one thousand inhabitants or more which, during any period of twelve consecutive months within the last decade, have been entirely free from typhoid fever. According to the United States Census Report for 1900, the typhoid death rate in this country was  $46\frac{1}{2}$  per 100,000 inhabitants. In 1908 the death toll from typhoid fever was no less than 35,000 in the United States.

*Vaccination*—Vaccination against typhoid fever is now a procedure of established worth. Its use began in 1896 when Pfeiffer and Kolle, and independently Wright, demonstrated that



*Bacillus typhosus* with faintly stained flagella. (Loeffler's method.)

persons injected with killed typhoid bacilli develop the same antibodies in their blood as are found in recovered cases of typhoid fever. Wright then introduced its use into the English Army and the results led to its introduction into other countries. In 1908 Major Russell of the United States Army was delegated to investigate the subject in all its aspects. He visited

Col. Leishman's laboratory at the Royal Army Medical College, London, and the Institute for Infectious Diseases, Berlin, for the purpose of studying the methods already in use. On returning to this country, he elaborated a method which combined the English and German methods.

Typhoid vaccination was begun voluntarily in the United States Army in 1909, the death rate per thousand that year being 0.28 among the enlisted men. In March, 1911, vaccination was made compulsory for all members of the service under forty-five years of age, and the death rate per thousand dropped to 0.03 in 1912. In 1913 the death rate from typhoid fever in the United States Army was 0, the number of cases per 100,000 being three, which occurred among the newly recruited men. The significance of the three cases of typhoid fever per hundred thousand men in the United States Army may be appreciated when one realizes that the civil death rate in the registration area of the United States was 16.5 per cent for the year 1912, this being the last year for which statistics have been published by the Census Bureau.

*Children*—Typhoid fever is essentially a dis-

ease of young persons. Of 1,000 deaths from typhoid fever collected from the registration area of the United States, one-third occurred in persons under twenty years of age and one-fifth in those under fifteen years. Typhoid vaccination among young children is increasing rapidly and, each year, more and more children are being vaccinated against typhoid fever. As a rule, the children do not have to remain home from school or indoors. Sometimes there is slight fever in the vaccinated children. Vaccination is well borne by children, the dose being proportioned to the body weight, taking 150 pounds as the unit.

#### **DIRECTIONS FOR USING TYPHOID VACCINE**

Three doses of the vaccine are given at 7 to 10-day intervals. The first dose contains 500 million bacteria, the second and third 1,000 million. In army practice, the 10-day interval is used as most desirable; but in civil practice, the 7-day interval is often more convenient, thus bringing the three doses on three successive Saturday afternoons. Experience has shown that the most suitable hour of the day for vaccinating is late in the afternoon, since the local

and general reactions do not appear usually until four or five hours after, at which time the patient is ready to retire; and, by morning, the entire reaction may have passed. It is wise to caution against active exercise—such as riding or tennis—on the following day, since it tends to aggravate the reaction. The first dose should not be given to women during or near the time of the menstrual period. The vaccine is injected subcutaneously, and not into the muscles or into the skin. This is necessary to secure slow absorption. Deep muscular injections, because of the rapid absorption, are more apt to produce severe reactions and pain on movement. The best location for the injection is the outer surface of the arm over the insertion of the deltoid muscle, where the subcutaneous tissue is abundant.

#### REACTION

Each dose of vaccine is followed by a local reaction which varies little, either with the size of the dose or the idiosyncrasy of the individual. Usually there is a red and tender site about two inches in diameter at the point of inoculation. This first appears in six or eight hours and reaches its full development in about twelve

hours and then gradually subsides, disappearing as a rule in 48 to 72 hours. Occasionally the red and swollen area may be quite extensive and extend from above the point of inoculation to the elbow. At times it also extends upward to the axilla, and the lymph nodes may be swollen and tender on pressure. The glandular swelling disappears in twenty-four to forty-eight hours and is never followed by permanent enlargement or suppuration.

The general reaction varies in its symptoms much more than the local. In children and in many adults it may be entirely absent. The milder form is characterized by a transitory headache and a feeling of weariness, lasting from a few hours to a day. In the average case the mild reaction resembles the feeling of discomfort associated with the onset of an attack of influenza. Moderate reactions are those characterized by a rise in temperature, which may reach 101 to 103 degrees F. Moderate reactions follow about 2½ per cent of all doses. General reactions more frequently follow the first than the other two doses.

*Immunity*—It has not yet been definitely established how long the immunity induced by the

prophylactic inoculation persists. Although the prophylactic vaccine has now been in use in the American service for over four years, there is as yet no indication of loss of immunity. The present practice in the United States Army is to revaccinate against both smallpox and typhoid fever at the commencement of each enlistment period, which is once in four years.

*Revaccination*—Revaccination should be performed more frequently in children than in adults. It is a good plan in vaccinating against typhoid fever to use the method used in smallpox; namely, to vaccinate once in infancy, once in childhood, once in youth, and once in adult life. This would probably give good protection.

*Practical Application*—Typhoid vaccination is carried out in almost all the larger hospitals of New York City; the nurses, the house staffs and the administration staffs being immunized. All male and female nurses and attendants of the Paris hospitals are compelled to be vaccinated against typhoid fever. The extension of this measure to certain phases of civil life is definitely indicated in the presence of an epidemic; or for those leaving their homes for

travel or for life in the country. It is especially recommended that children going away on vacations or to schools and colleges be vaccinated. Railroads and other industrial concerns that employ armies of labor, as well as individuals on farms and all persons who are compelled to live under unsupervised sanitary conditions, find in typhoid vaccination a great boon.

*Tuberculosis*—A fear has been expressed that typhoid vaccination may light up a latent tuberculosis. On this subject, Major Russel of the United States Army says: "Our statistics show that not only has the steady decrease in the number of cases of tuberculosis in the army been maintained, but that the decrease in the number of cases has been more rapid since the introduction of compulsory vaccination. This was, no doubt, due to the improved sanitary conditions and the greater care exercised in examining the recruits. In the annals of medicine there is only one campaign that can be compared to this one, and that is the practical extermination of smallpox by vaccination."

#### PARATYPHOID FEVER

The bacilli now recognized as paratyphosus

“A” and paratyphosus “B” were first described and studied by Achard and Bensaude. It is now conceded that about 3 per cent of the cases of so-called clinical typhoid fever are due to paratyphoid bacilli. According to the studies of the Johns Hopkins Hospital, 2 per cent of apparent typhoid cases were paratyphoid, while in Schottmuller’s study of 69 cases of apparent typhoid fever, 4 per cent were paratyphoid. Conrade, in a study of 250 cases supposed to be typhoid fever, found 29 to be paratyphoid fever. According to Jordan, type “B” paratyphoid bacillus is probably more widely distributed and is present in a majority of cases of paratyphoid fever. Proescher and Roddy, however, regard infection with paratyphoid “A” as more common in America, and Hoskins has reported an epidemic of 35 cases due to this bacillus. Most authors regard the type “B” as the most common cause of paratyphoid fever.

In many instances, infection has seemed to follow the ingestion of infected meat, especially pork. As a matter of fact, any article of food may contain the paratyphoid bacilli—such as ice cream, confectionery, oysters, public water supplies and milk. The type of infection produced

by the paratyphoid bacilli resembles a mild attack of typhoid fever.

Vaccine composed of the typhoid and paratyphoid bacilli has been used in several thousands of cases and no ill effects, other than the usual local reactions which follow after typhoid inoculation, have been seen. Such a combined vaccine immunizes the person against the two types of the paratyphoid bacilli, as well as against the typhoid bacillus. In view of the fact that the paratyphoid bacilli are so widely distributed, it would seem advisable to use the combined vaccine for immunizing purposes, inasmuch as such a vaccine protects against both types of the disease.

Paratyphoid Vaccines have been studied by Castellani, Cummins, Cumming, Kabeshima and others. The recent work of Kabeshima affords full evidence—both from animal experiments and from extended observations carried out on the personnel of the Imperial Japanese Navy—of the great protective value as well as the innocuous character of the paratyphoid inoculation. Kabeshima used a mixed vaccine containing equal numbers of the typhoid, paratyphoid “A” and paratyphoid “B” bacilli.

About 12,000 men have been inoculated with the mixed vaccine; and the results recorded in five naval hospitals in Japan during the period 1909 to 1911, after the introduction of inoculation with the mixed vaccine, show that adequate protection can be attained against the typhoid and paratyphoid bacilli.

Typhoid vaccination is not compulsory in the Italian army, but over 7,000 were vaccinated in 1913. The antityphoid vaccine was mixed with antiparatyphoid vaccine and the morbidity after one injection was 4.4 per thousand, after two, only 2.7, and after three injections, 0.3 per thousand; while the non-vaccinated developed typhoid or paratyphoid in 35.3 per thousand with a mortality of 7.1 per thousand.

#### DOSAGE OF COMBINED TYPHOID VACCINE

The combined vaccine is administered in three doses at intervals of seven to ten days, and the reactions resemble those which follow the use of plain typhoid vaccine. The initial dose contains 250 million of each of the paratyphoid bacilli "A" and "B", and 500 million of the typhoid bacilli. The second and third doses both contain double these amounts.

## Chapter XVII

### CHOLERA AND PLAGUE

#### CHOLERA

*Prevalence*—Asiatic cholera occurs in the form of epidemics which follow the paths of human traffic, spread quickly over wide areas, and kill from 25 to 50 per cent of those affected. No disease showing these features and, at the same time, presenting a definite tendency to epidemic distribution, appeared in the civilized world before the beginning of the nineteenth century. Since then it has repeatedly encircled the earth. Scarcely a country has escaped. All such regions as are reached from India by a long sea trip, such as Australia, Cape Colony and the unfrequented regions of the Arctic Zone, remain free. The origin of cholera epidemics has always been India—its real home—and more persistently the lowlands of Bengal, with Calcutta for the chief city.

*Vaccination*—Attempts to protect human beings against cholera by prophylactic vaccination were made as early as 1885 by Ferran, a

pupil of Pasteur. Under the influence of the French school and its endeavors to immunize with living attenuated microorganisms, Ferran applied similar methods to cholera by inoculating with small quantities of living broth cultures of the cholera spirilla. The method which Haffkine worked out, some years after Ferran's experiments, also depended upon the injection of living cultures; but Haffkine attempted to produce two separate vaccines, one attenuated, the other enhanced in virulence. Beginning his work as early as 1893, Haffkine and others vaccinated as many as 40,000 people in India. On the whole, the results obtained were very encouraging.

According to Zinsser, we have reason to believe that immunization with killed cultures may produce results fully as efficacious. At present it is not to be expected that we could produce by active artificial immunization an immunity as permanent as that which results from an attack of the disease. Later on, Kolle recommended the injection of killed cholera spirilla, and good results with Kolle's method have been reported from Japan. Kolle's method is more practicable. Two doses of the vaccine are given

at intervals of ten days, and the duration of immunity is about one year. The first dose contains 500 million killed bacteria, and the second dose 1,000 million.

*Results*—Haffkine found a considerable reduction in the incidence of the disease, but no reduction in mortality among the inoculated persons who became infected. The degree of protection seemed to increase during the first four days and to last about fourteen months. During the Japanese epidemic of 1902 there were 77,907 persons vaccinated. The mortality was reduced from 75 per cent to 42 per cent. In Bilibid prison, Strong inoculated over one-half the inmates, some 1,838 persons, among whom four cases of cholera subsequently appeared. Immunization will in no sense replace sanitary measures in repressing cholera, but apparently it is useful in regions where the disease has already broken out. Since 1896 the Indian Government has maintained a regular station for the vaccination of coolies in order to prevent the spread of the disease.

#### PLAGUE

*Prevalence*—The history of bubonic plague can be traced back to the third century. In

Justinian's reign, a great epidemic spread over the Roman Empire and, before it terminated, it had destroyed over 50 per cent of the people. In the fourteenth century, the whole of Arabia was stricken with this "black death." Europe and America have been practically free from the disease. In spite of all efforts to stamp it out, plague still breaks out in all its horrors so that at the present time over 500,000 persons die annually from it.

*Vaccination*—*Haffkine's prophylactic* consists of killed cultures of the plague bacillus injected subcutaneously in two doses at intervals of ten days. The first dose contains 500 million bacteria and the second dose 1,000 million. The reactions which follow vaccination with Plague Vaccine are sometimes marked. The symptoms may consist of a rise of temperature to 102 degrees F., malaise, depression, headache, and swelling and pain at the site of inoculation. The symptoms usually pass off in 24 to 48 hours. The prophylactic vaccine has been used on a large scale by Haffkine in India, by Strong in the Philippines and, to a large extent, by others in many parts of the world during plague epidemics.

*Practical Application*—Active immunization of the community, in the face of an epidemic, is a valuable addition to our preventive measures against plague. It is of first importance as a protective measure in small communities, on shipboard, in camps, barracks, at quarantine stations, at plague laboratories, among rat brigades, as well as for physicians, nurses and others who are exposed. The active immunity produced by vaccination with Haffkine's prophylactic lasts from one to six months.

*Results*—During an epidemic in the Punjab, about one-third of the population of fifty villages was inoculated, the mortality being 16.9 per cent as compared to 45.2 per cent in those not inoculated. According to Kolmer, mortality among the inoculated is much lower, being 11 per cent to 41 per cent as compared with 50 per cent to 92 per cent among the non-immunized.

## Chapter XVIII

### WHOOPIING-COUGH, SCARLET FEVER AND CEREBROSPINAL MENINGITIS

#### WHOOPIING-COUGH

*Prevalence*—More than ten thousand children in America die every year from whooping-cough. Under one year of age the mortality is 27 per cent. According to Osler, in the year 1900 there were 9,958 deaths from whooping-cough. About 80 per cent of the fatal cases were under two years of age. The fatal issue in whooping-cough is usually caused by the complication of broncho-pneumonia, nine-tenths of the deaths being due to this complication. The records of the New York City Department of Health show that from February to August, 1913, there were 2,451 cases of whooping-cough reported. It has been estimated that the death toll from whooping-cough in England and Wales is greater than the mortality from measles, scarlet fever and diphtheria. The greatest susceptibility is from six months to five years of age, and over half of the cases occur during the

first two years of life. Almost everybody is susceptible and the majority of persons have the disease sometime during their life. Susceptibility decreases with age, but it may be seen in adult life and even in old people.

*Cause*—The cause of whooping-cough is a small bacillus first described by Bordet and Gengou in 1900 and isolated in pure culture by Bordet in 1905. The bacillus is called *Bacillus pertussis* or sometimes the Bordet bacillus. The causal relation of the Bordet bacillus to whooping-cough was demonstrated by Mallory, who examined the trachea and lungs of three patients that died of whooping-cough in the Boston City Hospital. Moreover, Mallory successfully inoculated animals and produced the typical disease, and succeeded in recovering the bacillus in pure culture from the tissues of the animal after it was killed.

*Vaccination*—Any means for efficient prophylaxis against whooping-cough is of inestimable value. While the use of a vaccine for prophylaxis against this disease is rather recent, nevertheless it has already attained a place for itself in immunology and has demonstrated the rationale of thus immunizing against the dis-

ease. Children in families in which other members are suffering from whooping-cough, or those who are otherwise liable to exposure, should be given immunizing doses of Pertussis Vaccine, prepared from the Bordet bacillus. Dr. E. Mather Sill, of New York, and others have used this vaccine in a series of children in families where other members were suffering from whooping-cough and, although closely observed for over two months, the children did not develop the disease.

*Dosage*—Three doses of the vaccine are given at intervals of seven days. The first dose contains 25 million bacteria; the second 50 million and the third 100 million.

*Reaction*—The clinical reaction after an injection of the vaccine is similar to that following the use of other prophylactic vaccines, although the reaction is usually less marked. The local reaction consists of redness, swelling, and slight tenderness at the point of inoculation. Occasionally there is a rise in temperature of one to three degrees. The symptoms usually pass off after 24 hours.

*Immunity*—It has been the general experience of clinicians that, when a child is already in the

stage of incubation, the vaccine will not prevent the development of the disease; but where the child is not in the stage of incubation but about to be exposed, the prophylactic vaccine will afford immunity for at least two or three months and probably for a longer time.

### SCARLET FEVER

*Prevalence*—The seasonal prevalence of scarlet fever resembles that of diphtheria, increasing in the fall of the year, due in part to the gathering of children in the schools. There is probably always more or less scarlet fever in any thickly settled district in the temperate zone. Scarlet fever varies greatly in intensity in different epidemics. In some epidemics the death rate, according to Rosenau, is 30 per cent; in others, it varies from 4 to 15 per cent. In England and Germany the disease is always endemic and frequently epidemic. In the northern part of the United States, scarlet fever is much more prevalent than in southern portions. It has been noticed in the northern states that once in every six years there is a general epidemic of this disease which frequently assumes a malignant type.

*Cause*—The cause of scarlet fever is not known. Klein in 1885 was the first to advocate the streptococcus as the specific cause of scarlet fever. This microörganism is constantly found in the throat of scarlet fever patients and can be isolated from the blood of scarlet fever patients during life and almost constantly after death; and, in the majority of cases of scarlet fever, the cause of the complications and death is the streptococcus. It is probable, however, that the streptococcus plays a secondary rôle in scarlet fever as it does in smallpox. The disease itself may be due to a protozoan-like body described by Mallory, which lowers the resistance of the body to streptococcic invasion. There is good reason to believe—as pointed out by Hektoen, Jochmann and others—that, although the streptococcus is undoubtedly closely associated with the disease, it is the cause of the complicating angina which so often arises, rather than the scarlet fever itself. It is generally accepted that the streptococcus is always associated with scarlet fever, both in the throat and in the septic complications.

*Vaccination*—Most of the work of vaccination against scarlet fever with *Streptococcus*

Vaccines has been done by Russians, led by Gabritschewsy (*Berliner klin. Wochensch.*, 1907, XLIV, 556). Nearly all of the published accounts are in Russian, so that the method has attracted comparatively little attention of the profession generally. More than 50,000 cases are on record which have been successfully protected with the Streptococcus Vaccines, which are prepared from streptococci isolated only from cases of scarlet fever. It is claimed that after three injections of the vaccine and usually after two, a complete immunity is established against scarlet fever, lasting probably about a year and a half. The vaccination is contraindicated in very young infants or in persons greatly prostrated from any cause, such as nephritis.

*Dosage*—The injections are given at intervals of seven days. The first dose contains 250 million killed bacteria; the second dose contains 500 million; and the third dose 1,000 million.

*Reaction*—In most cases there appears at the site of the primary injection, about 24 hours after it is given, an area of redness and infiltration, somewhat painful and tender and lasting a few days. With this is also associ-

ated a slight rise in temperature. In about 10 to 15 per cent of the cases, an erythematous eruption resembling scarlet fever appears at the site of injection and sometimes extends over most of the body; in which case there may be associated angina, swelling of the lymph glands and strawberry tongue. Reactions after the second and third injections are less severe.

*Results*—Statistics furnished by the Russian workers appear to speak very strongly of the value of the prophylactic vaccination. Smirnofff used the vaccine in thirteen small villages in Russia where the sanitary conditions were very poor and where there was no possibility of quarantine. He vaccinated 455 people and every one who received three full injections was protected against the disease. In villages without vaccination, 20 per cent contracted the disease and 11 per cent died; in villages with vaccination, 3 per cent contracted the disease and none died. In an epidemic in Kharkov, 610 people were inoculated by Yemelyanoff and not a single person contracted the disease. Zelikin used the vaccine in country practice during a severe epidemic and, among 613 people who received only two injections of the vaccine, none

contracted scarlet fever. From these published accounts it would seem that a streptococcus vaccine, used as prophylaxis for scarlet fever, is destined to materially aid in controlling epidemics of scarlet fever, and this method should be given wider application in this country.

### CEREBROSPINAL MENINGITIS

The prevalence and severity of epidemic cerebrospinal meningitis have already been dwelt upon (See page 137). The prevention of this disease by immunization with Meningococcus Vaccine has only recently been given serious consideration.

*Vaccination*—During the height of the 1912 Texas epidemic, Dr. Sophian, formerly of the New York City Health Department, advocated the use of prophylactic vaccination since the disease was spreading in spite of all measures employed. Several hundred people were inoculated within a period of about six weeks. Almost all of those who were vaccinated had been exposed to the disease, many being doctors and nurses who were in constant touch with the sick. None of those who were fully vaccinated with three doses developed the disease.

*Immunity*—At the end of the epidemic, Sophian and Black carried out experimental prophylactic vaccinations on eleven students in the Southwestern Medical College using varying doses of Meningococcus Vaccine. Subsequently Black carried out complement fixation tests on eight of the original students, and was able to demonstrate immunity at the end of one year as a result of the vaccination. More recently (*The Journal A. M. A.*, December 12, 1914), Black carried out complement fixation tests on the serum of seven of the vaccinated students and showed that a high degree of immunity still persisted at the end of two years after the date of vaccination. It seems a justifiable conclusion that persons prophylactically vaccinated may safely consider themselves immune for at least two years.

*Dosage*—The dosage established by Sophian and Black consists of 500 million killed meningococci as the first dose; 1,000 million for the second and third doses, the injections being given at 7 to 10-day intervals.

*Reaction*—The local reaction is very much the same as obtains after injections of other bacterial vaccines, notably Typhoid Vaccine. A

few hours after injection there are redness, swelling and tenderness at the point of inoculation. Some subjects react more severely than others. Pain in any marked degree rarely lasts more than a few hours. General constitutional symptoms are frequently missing. Most often the patient complains of moderate headache and general malaise, and the temperature rises from one to three degrees. Sometimes, however, the temperature may rise to 104 degrees F., and the patient may suffer from nausea and have bodily pain, and may vomit.

*Results*—During 1913, Texas had a moderate amount of meningitis, though it was really free from an epidemic. Vaccine was used in quite a considerable number of people. It was employed both in civil communities and in institutions. According to Sophian, there were at least 5,000 people vaccinated and he could find no record of meningitis developing among those vaccinated. In the same year, quite severe epidemics occurred in Tennessee, Arkansas and Nebraska. Prophylactic vaccination was liberally employed in six communities and, as far as can be learned from reports, the vaccinations were successful. Major Wadham of the

United States Army (*Military Surgeon*, August, 1913) successfully protected 600 people with Meningococcus Vaccine during an epidemic of meningitis at Deckerville, Arkansas, following the floods in the Ohio and Mississippi Valleys. While observations must be made in many thousands of cases before any positive deductions are warranted, the clinical data so far, however, are encouraging.

## Chapter XIX

### HAY FEVER

*Historic*—The medical writers of the sixteenth, seventeenth and eighteenth centuries mentioned the existence of a certain form of catarrh of the mucous membranes, of annual and seasonal periodicity, which was correlated in some way with the flowering period of plants; but the recognition and establishment of hay fever as a true clinical entity is accredited to John Bostock (*Medico-Chirurgical Transactions*, London, 1819, x, 161). The first definite connection between the pollen of grasses and hay fever was recognized by John Elliotson (*The Lancet*, 1830, II, 370) in 1830. The medical world is indebted to Dunbar (*Zur Ursache und Specifischen Heilung des Heufiebers*, Muenchen, 1903) for the exhaustive scientific proof of the specific action of pollen as the causative factor of hay fever.

The work of Noon (*The Lancet*, June 10, 1911, 814), Freeman (*The Lancet*, September 16, 1911, 1572), Clowes (*Proc. Soc. Exp. Biology*

and *Medicine*, 1913; x, 70), Lowdermilk (*The Journal A. M. A.*, July 11, 1914, 141), Manning (*The Journal A. M. A.*, Feb. 20, 1915, 655), Freeman (*The Lancet*, April 25, 1914, 1178) Oppenheimer and Gottlieb (*N. Y. Medical Journal*, Feb. 6, 1915, 229), and especially the recent work of Koessler (*Illinois Medical Journal*, August, 1914, 120), has demonstrated the practicability and clinical value of active immunization against hay fever by means of pollen extracts. Clowes was the first to report a definite method of vaccination against hay fever in this country, and his work stimulated extensive study of this form of active immunization which has now been placed on a more complete basis by Koessler.

#### RESULTS OF VACCINATION

Clowes vaccinated 8 patients, all of whom experienced a marked alleviation of general symptoms. Of the 84 cases reported by Freeman, 64.6 per cent were completely cured or markedly improved; 23.9 per cent of the cases showed slight improvement, while 11.5 per cent were not benefited. Twenty-one cases have been reported by Manning and of these, fourteen were objectively and subjectively relieved; in the

other seven, the treatment was incomplete but four of these had milder attacks. Lowdermilk reports 19 cases, with successful results in 16. Koessler has treated 41 hay fever patients by active immunization with Pollen Vaccine and reports four completely cured; 29 markedly improved subjectively and objectively; 5 were subjectively improved, while the remaining 3 were not affected. Oppenheimer and Gottlieb treated 11 patients before and during the hay fever season: altogether there were 5 cures, and marked improvement occurred in 4 cases; while 2 of the cases showed no improvement.

Marked improvement consists in later, milder and shorter attacks; in the possibility of remaining in town and at work for the first time in years; and in a diminution or disappearance of the troublesome cough and constitutional symptoms.

#### POLLEN VACCINE

*Description of Vaccine*—While the results obtained by the above-mentioned investigators have demonstrated the efficiency of Pollen Vaccine, yet their work has also shown that watery extracts of pollen are unstable and rapidly deteriorate, losing their potency after about three

weeks. Therefore, it has not been possible heretofore to market Pollen Vaccine commercially. By experimentation with different means of extracting the pollen, a method has been evolved in our laboratories of making the extraction in glycerin and salt which yields a vaccine that has been demonstrated to remain stable without any detectable loss in potency for a period longer than the time required to administer the complete prophylactic treatment.

In the preparation of Pollen Vaccine, the pollen from the various common grasses, weeds and other flowering plants which cause hay fever in the spring and in the fall, have been combined. The correct amounts of vaccine for the various doses are supplied in individual vials serially numbered, each vial containing approximately one-tenth cubic centimeter of the vaccine. Before administration, the vaccine must be diluted with the diluent which is furnished in a separate vial; but this final dilution should not be made until immediately before administration of the vaccine.

*Dosage and Administration*—The prophylactic treatment consists of 15 doses of Pollen Vaccine administered subcutaneously—in the ab-

dominal wall, in the interscapular region, or at the insertion of the deltoid muscle—using the same careful asepsis as for any hypodermic injection.

The interval between doses is usually one or two days, a convenient plan being to give three doses per week.

*Duration of Treatment*—The duration of the prophylactic treatment should, on the average, consume from four to six weeks. In the great majority of cases that have been reported, reactions from the vaccine have not been noted and it is possible to proceed with the immunization at the intervals stated above. If, however, severe reactions are encountered, the immunization should be continued and completed, using longer intervals between doses.

#### PERIODS OF HAY FEVER

In the United States, hay fever appears at two distinct periods of the year—one, beginning about the last week in May and continuing until the second week in July (the so-called “rose cold”); the other (known as the American form of hay fever), commences about the second week in August and continues until the first week in October. The spring variety is caused by the

pollen of grasses, notably timothy, rye, red top, June grass, etc.; while the autumnal form is induced by the pollen of ragweed, golden-rod, Indian corn, etc.

#### TIME TO VACCINATE

It is highly desirable that the treatment be a strictly prophylactic one, although encouraging results have been obtained with active immunization when carried out after the disease was already developed. Since it is desirable that a maximum immunity be established before the hay fever season sets in, it is recommended that the prophylactic inoculations be given at least 8 to 10 weeks before the time for the annual onset. If this is not possible, prophylactic treatment may be begun at any time before the onset of the disease or even after the disease has started; using longer intervals between injections to avoid severe reactions, in case the patient is already suffering with hay fever.

*Caution*—In the early stages of immunization it is possible by an overdose to induce a severe attack of hay fever lasting nearly 24 hours. In the later stages, however, this has not been observed. Therefore, it is important to follow

the progressive dosage and to allow a sufficient interval between the doses.

*Reaction*—The doses of Pollen Vaccine, as prepared in our laboratories for the prophylactic treatment of hay fever, have been so adjusted as to avoid severe reactions. Well-marked reactions, characterized by an exaggeration of the usual symptoms of hay fever (sneezing, lacrimation, itching of the eyes, cough, dyspnea in asthmatic subjects, and sometimes edema and urticaria), which have been met with by some workers, have occurred only as the result of too large an initial dose.

According to Koessler, only a very small number of patients show any local reaction at the site of injection, consisting of a slight reddish-colored tumefaction.

*Immunity*—The immunity does not last equally long in all patients. According to Freeman, the immunity acquired from the prophylactic inoculations seems to last at least one year after the treatment has been discontinued. Koessler observed that the susceptibility of patients who received the prophylactic inoculations before the onset of the hay fever season returned during the fall and winter; so that,

in the following spring, the active immunization had to be repeated in order to protect the individual from an attack during the next hay fever season. This emphasizes the fact that patients must return each year for several years, if the prophylactic treatment is to have a permanent influence on their susceptibility to hay fever.

*Some General Principles*—(1) Patients with marked constitutional disturbances including asthma, apparently derive greater benefit from the prophylactic inoculations than patients with slight and local symptoms. (2) Age makes no difference in the benefit derived from the prophylactic treatment.

*Treatment during Attack*—While it is most desirable and recommended by all workers that the inoculations be strictly prophylactic—that is, that they be given prior to the onset of the hay fever season—yet several investigators have used the Pollen Vaccine for treating patients during an actual attack of hay fever. Thus, Lowdermilk treated 16 patients after the onset of the actual attack and 13 of them were cured; the 3 not benefited all began treatment more than a month after the onset of symptoms.

The 21 cases reported by Manning were patients who were already suffering from the disease, and 14 of them were relieved objectively and subjectively. Of the cases treated by Oppenheimer and Gottlieb, 5 were treated during the attack; and of these, 4 were promptly cured, while the other patient received no benefit.

If the vaccine is administered during the attack of hay fever, it is important that the doses be sufficiently spaced to prevent a severe reaction. For this reason, most workers have adopted intervals of 3 to 10 days.

*How to Secure Treatment*—Pollen Vaccine as prepared in our laboratories has been demonstrated to retain its potency unimpaired for a period which is longer than the time necessary to administer the complete prophylactic treatment. The period of potency is stamped on each package. The vaccine for each case to be treated should be obtained by direct shipment from the laboratories at the time when the physician desires to begin the treatment; and the treatment should be started promptly in order to be completed before the expiration date stamped on the package.

# Part V

## VACCINES IN THE TREATMENT OF DISEASE

### Chapter XX

#### THERAPEUTIC INOCULATION

*Important Points*—The trend of all modern therapy of infectious diseases is toward the elaboration of specific measures which will directly influence and counteract the infectious agent. The purpose of vaccines in treating disease is to stimulate the patient's tissue-cells to produce immune bodies in larger quantities than the cells themselves have been able to generate under the stimulus of the infection. The tissue-cells in the infected area become so intoxicated with the foreign substances produced by the infection, that they are not able to generate antibodies in sufficient numbers to combat the disease. By stimulating the cells in other parts of the body, antibodies are produced which are carried by the tissue fluids to the focus of the

disease and thus aid the infected tissue-cells in overcoming the infection.

We desire to emphasize the following points in vaccine therapy: (1) Every case must be individually studied—just as when administering drugs—and the size, number and frequency of doses must be adapted to the needs of the individual case. (2) The necessary medical and surgical measures must not be neglected, for reliance should not be placed solely on the action of the vaccine. (3) Vaccines have failed in many instances to give the desired results because they were given in cases unsuited to vaccine therapy. (4) Vaccines must not be expected to construct tissues that have been destroyed by pathogenic bacteria. (5) To be effective, vaccines must be timely and intelligently administered.

*Negative Phase*—When Wright announced his theory of the negative phase and the increased risk to infection during the period of this phase, progress in vaccine therapy for a time was checked. Accumulative practical experience of Sir William B. Leishmann of the English Army, however, enabled him to refute this theory most emphatically, and to prove con-

clusively that, with correct dosage, whatever force it had was more theoretical than real, and that the most important evidence must come from actual experience rather than from laboratory experiment. Pfeiffer and Friedberger disproved the presence of a negative phase in laboratory tests on guinea-pigs, as did Leishman in 100 patients at the Baring Asylum. Wright himself since 1909 has receded to a very great degree from his position concerning a negative phase.

*Application*—The enthusiastic supporters of therapeutic inoculation stretch the possible application of bacterial vaccines to cover the treatment for all diseases; and they attempt to show that the introduction of large numbers of extraneous bacteria stimulates the natural immunizing processes to greater activity, thus artificially fostering the slow process of naturally acquired immunity. Such enthusiasts lose sight of the fact that there is no common mechanism of immunization. The process differs not only according to the type of infecting agent, but also according to its virulence; and failure of the infected host to respond by effective defensive processes, also plays an important part. No

more important principle has resulted from studies in immunology than that the process of immunity in each infection must be studied by itself; hence, a definite method of procedure must be adopted in every individual case.

*Dosage*—The importance of small doses of vaccine, such as would give the maximum opsonic response, and the necessity of giving successive doses at sufficient intervals of time to allow the development of the maximum reaction from the previous inoculation, were emphasized repeatedly by Wright. The principles of the therapeutic use of bacterial inoculations were developed from careful studies of subacute and chronic localized infections, in which the focus of infection was more or less walled off from the rest of the body and in which phagocytosis occupied a prominent place in the pathologic changes in the focus of infection.

While the dose should not be too large, neither should it be too small. There is a proper dose for each patient, and this may be determined by starting with a small dose and gradually increasing it until some reaction is secured. An efficient dose may produce some reaction, and increased doses are contraindicated so long as

any sign of general or focal reaction is produced and so long as steady progress is maintained.

#### CLINICAL EVIDENCE REGARDING THERAPEUTIC INOCULATION

If improvement occurs regularly after a given treatment, when used in cases in which improvement does not usually occur so quickly, we have some reason to believe that the measure has therapeutic value. In any individual case, the question as to whether such improvement occurred is necessarily decided by the judgment of the physician whose conclusions are based in turn on his experience in other similar cases and on his accuracy of observation. There are, however, so many undeterminable and recognized factors which influence the outcome of any individual case that case reports covering a small number of observations offer very little assistance in determining the value of a method, particularly when we remember that there is always a tendency to report favorable cases and to allow the unfavorable to pass unnoticed. Only when large groups of cases—accompanied by adequate control cases—are available, can

clinical evidence approach in reliability that of animal experimentation.

In certain strictly localized and in chronic infections, there is abundant clinical evidence that the infectious process may be favorably influenced by bacterial vaccine inoculations. Under general infections may be included those diseases, such as streptococcic septicemia, in which there is a profound disturbance of the physiology of the entire body—as evidenced by fever, and other signs of sepsis—and in which a more or less bacterial invasion of the blood is demonstrable.

The treatment of this class of cases by vaccines has not been followed by clinical results which justify the method as a routine procedure. In puerperal sepsis, adequately controlled case reports are few; and the consensus of opinion has been that the favorable outcome of the treated cases could be attributed as well to the normal variability of the disease, as to the specific method of treatment. The bad effects of stimulating to increased activity the tissue-cells, which already are overtaxed with toxic substances, may be as evident to the careful clinician as to the serologist. In general, it may be

stated that the more closely the case approaches a strictly localized infection, the more likely is it to prove amenable to vaccine treatment.

According to Sondern of New York City, vaccine therapy in acute general infections is still open to question from a theoretical standpoint, and should be considered as purely experimental; but bacterial vaccines have proved of value in cases of localized and chronic infections.

#### REACTIONS FOLLOWING VACCINES

The inoculation of specific bacterial vaccines into an individual suffering from an infectious disease is followed by clinical changes in the disease which constitute what is known as a "reaction." These changes may be: (1) Local, at the site of inoculation, including edema and erythema; (2) Focal, at the site of localization of the infection, such as increased pain and swelling in joints; (3) General, including fever, leukocytosis, malaise and headache. The clinical reactions have been extensively employed in diagnosis and have proved of service in the regulation of the dose and interval of the inoculations in the treatment of diseases by active immunization.

The definition of the degree of reaction which indicates the optimum dose of vaccine has occasioned much discussion, some arguing that the slightest reaction is the optimum, others that more marked reactions are advisable. Experience teaches that, in general, severe reactions are to be avoided in all cases. Each disease presents special problems in this respect and, in any disease, the individual case must be considered. In general, if there is any question as to the strict localization of the process, any reaction in excess of a moderate local redness or slight febrile reaction is to be regarded as a warning that the dose should be decreased or at least not increased.

#### SURGICAL MEASURES

The inoculation of bacterial vaccines for the treatment of local infections, like other procedures in medicine, has been employed under conditions not contemplated by those who devised it, to the neglect of older and approved methods of treatment. The attempt by inoculation of vaccines to promote the healing of an acute abscess, in which incision and evacuation of pus is necessary, shows a total misapprehension of

the principles of therapeutic inoculation and, besides, is wasteful of the time and energy of the patient. Chronic metastatic infections arising from some primary suppurative focus call first for surgical treatment of the primary lesion, if possible; and, later, the use of vaccines may be considered. The vaccine treatment of suppurating sinuses has been widely advocated and may prove of benefit, but first of all the physician should put into practice the old surgical maxim that when a sinus fails to heal, it is well to ascertain whether there is not some foreign body at the other end.

#### INDICATIONS FOR THERAPEUTIC INOCULATION

Infectious processes in general are suitable for vaccine treatment (1) if they are localized; (2) if they are more or less chronic; and (3) if adequate surgical measures have been applied. Any departure from this definition makes the indications for vaccine treatment less clear, though it is conceded that many instances are daily met with that make the trained immunologist feel justified in extending his efforts beyond these limits along experimental lines.

Almost from the beginning of bacterial ther-

apy, the belief has been repeatedly expressed that little can be expected of bacterial vaccines in generalized infections. So far as present knowledge takes us in such infections, the tissue-cells are busily engaged in combating the poisonous groups resulting from the death of the bacterial cells in considerable quantity in the body. In most instances, their efforts are successful and recovery takes place. To thwart their efforts by adding more bacterial protein, when already worked to capacity, would appear unjustifiable.

#### PREPARATION OF BACTERIAL VACCINES

Bacterial vaccines are prepared in our laboratories from cultures of pathogenic bacteria which have been grown upon suitable solid media under the most favorable conditions. Several strains of the respective bacteria are used; for it has been demonstrated clinically, as well as in the laboratory, that different cultures of the same microorganism may vary widely in biochemic properties; and that most vaccines should be polyvalent in order to possess the greatest efficiency. *Polyvalent* means that the suspension contains several cultures of the

same species of bacteria—that is, several “strains” of the microörganism are used—the cultures being obtained from many different sources of infection in which that species of bacteria is found.

The bacterial cultures are suspended in physiologic salt solution and thoroughly shaken to separate the microörganisms; the bacterial suspension is subjected to a careful count; the bacteria are killed by heating the suspension and by the addition, after cooling, of 0.25 per cent trikresol. The suspension is then diluted with sterile physiologic salt solution containing 0.25 per cent trikesol until each cubic centimeter contains the desired number of bacteria.

#### AUTOGENOUS vs. STOCK VACCINES

A great deal of discussion has arisen regarding the question as to whether it is advisable to use autogenous vaccines—that is, vaccines that are prepared from cultures of the bacteria obtained from the patient; or whether it is better to make use of stock vaccines prepared from cultures of the microörganisms causing the infection, but not derived from the particular individual to be treated. As long as we know so little of what vaccines may accomplish, it is

clear that our clinical knowledge is not sufficient to decide such a question. We can only speak theoretically, and theoretically we must admit the existence of many strains of a given type of microorganism and also the possibility of individual differences in the microorganisms. Upon this basis, autogenous vaccines would appear to be preferable to stock vaccines, since autogenous cultures comply with the scientific requirements of a vaccine.

From a practical standpoint, however, stock vaccines are more satisfactory to use for various reasons: (1) It is frequently impossible to prepare an autogenous vaccine for lack of proper facilities. (2) It requires several days to prepare an autogenous vaccine and this necessitates loss of valuable time in the treatment. (3) Since it has been demonstrated that different cultures of the same species of bacteria vary widely in their immunologic properties, it is obvious that a polyvalent stock vaccine will produce an immunity which will be efficient for a very large majority of infections caused by that specific type of microorganism. (4) An autogenous vaccine adds materially to the cost of an otherwise inexpensive treatment.

## DOSAGE OF BACTERIAL VACCINES

Wright expressed the opinion that, by following the opsonic curve, indications might be obtained for the introduction of vaccines both as regards the size of the dose and the frequency of the injections. Suffice it to say, however, that the opsonic index unfortunately has not fulfilled those expectations with which it was first greeted; and that any attempts at vaccine treatment must still be made upon a more or less empiric basis, and with no more definite and accurate methods of dosage and frequency of injection than is afforded by clinical symptoms. But even so, there can be no doubt that a certain amount of good may be accomplished; how much, it is as yet impossible to say. So much depends upon individual cases, the personal factor of the observer, etc., that conclusions can only be drawn with great care. As yet, we do not know enough of what may or may not be accomplished to warrant any dogmatic statement.

*The general rule in vaccine therapy is to begin with small doses and progressively increase; immunity being more effectively produced by repeated injections of gradually in-*

creasing doses than by a single injection of a large dose. At the same time, the clinical effects in the individual case must be made the basis for the size and frequency of the doses; for the dosage is influenced by the nature of the infection, and also by the individual susceptibility. Should no improvement be noted, and the clinical reaction permits, the size of the dose may be increased or the intervals shortened, or both. If a pronounced clinical reaction occurs—characterized by fever and aggravation of local symptoms—it indicates that the dose has been too large, and the next injection should be smaller.

The amount of vaccine required varies according to the age and personal characteristics of the patient; and the type, duration, extent and severity of the infection. It is important to bear in mind, however, that the packages containing four or six different dilutions, as marketed by most laboratories, do not in any sense constitute a complete treatment. It is impossible to prepare any four or six graduated doses which will meet the conditions of every case; some cases might require fifteen or more doses, while four might suffice for others.

As a general rule, the intervals between the doses in acute infections vary from one to three days. After the acute symptoms have subsided—as shown by a drop in the temperature and by other signs of improvement—the intervals may vary from two to five days. In subacute and chronic infections, the vaccine should be given every four to seven days; the doses being increased according to the clinical symptoms.

#### MIXED VACCINES

Cases are frequently met with in which more than one microorganism seems to be concerned in the pathologic process, and for these cases combined or mixed vaccines containing all the bacteria seems desirable. The use of mixed vaccines should, however, be restricted to those cases in which careful studies have been made and the bacteriology of the infection determined. Active immunization has been brought into disrepute by attempts to utilize vaccines as a cure-all in diseases in which there is no evidence that they are of value; in those of undetermined infectious origin; and in those in which there is no evident infectious cause. In consideration of the scientific basis of active im-

munization, this misuse of vaccines is reprehensible and deplorable; it is injurious to the unfortunate patient and demoralizing to the physician.

*There is, however, a distinct field for mixed vaccines.* In exposed parts of the body—such as the upper respiratory passages and the genito-urinary tract—the bacteria normally present become complicating factors in any morbid condition produced by an infective agent. These bacteria, unable ordinarily to overcome the resistance of the body, find the condition resulting from a lowered vitality suitable for rapid growth; and they become additional offensive factors or lead to further complications. (1) *In whooping-cough*, for example, the Bordet bacillus sets up a condition in the respiratory tract which enables the pneumococcus, influenza bacillus, streptococcus, staphylococcus and other bacteria commonly present, to become pathogenic: and they continue to produce symptoms long after the whooping-cough bacillus has been overgrown. (2) After the first few days in a case of *gonorrhoea*, the staphylococcus is found almost to the exclusion of the gonococcus. Hence, Gonococcus Vaccine will not adequately

control the condition in subacute and chronic cases; and it is best, therefore, to use a combined vaccine. (3) Again, *pneumonia* is caused chiefly by the pneumococcus; but when pneumonia follows some suppurative condition, the streptococcus and staphylococcus are associated with the pneumococcus. Hence, a combined vaccine is indicated. (4) In *diseases of the respiratory tract*, the micrococcus catarrhalis or the Friedlander bacillus causes the primary infection; but after secretion has continued a few days the pneumococcus, streptococcus and staphylococcus are invariably found. Hence, a combined vaccine is indicated for both the acute and the chronic conditions.

It is always desirable, however, that a bacteriologic examination be made to determine the causative microorganism before using a vaccine, in order that the action of the vaccine may be specific; but it is not always practicable for such an examination to be made and, in most cases, a correct diagnosis may be made from the clinical symptoms.

#### WHEN TO USE VACCINES AND WHEN SERA

When the vitality of the patient is low—that

is, when the resisting power is such that the patient cannot produce sufficient antibodies—it becomes necessary to supply these immune bodies by the administration of serum. For example, in a severe case of pneumonia, the patient's tissue-cells have sufficient to do to maintain the vitality of the body; and, if called upon to produce antibodies by being stimulated with a bacterial vaccine, the tissue-cells would be overburdened and immunity would not follow. In such cases, the administration of an immune serum furnishes the patient with antibodies already formed, and thus combats the diseased process; while the patient's tissue-cells are permitted to exert all their energies toward maintaining the vitality of the patient. In a general way, it may be said that the best results in acute general infections are obtained from the use of sera rather than vaccines.

The greatest field for the application of vaccines in the treatment of disease is in certain strictly localized infections, and in chronic infections.

## Chapter XXI

### CUTANEOUS DISEASES

Since Wright first applied the principles of vaccine therapy to furunculosis and sycosis, vaccines have been used in a number of other cutaneous disorders with varying results. Vaccine therapy has its indications and is of unquestionable value in certain conditions when administered properly. Its value and beneficial results are most noticeable in chronic or recurrent types of staphylococcic infections, such as acne, furunculosis, sycosis vulgaris, etc. In certain types of acne vulgaris, Acne Vaccine has proved its value; yet in these conditions vaccine therapy frequently fails to produce beneficial results and is due in all probability, as Wright believes, to the failure of the immunizing mechanism of the patient to produce antibodies. In the vaccine treatment of cutaneous disorders certain important factors must be considered, such as the dosage, interval between inoculations, individual susceptibility, etc. It may be formulated as a general rule and a rigid

one that, *in treating any skin disease with bacterial vaccines, the initial dose must be small.*

### ACNE

Acne may be divided into two classes; the non-pustular variety in which comedones are the predominating lesions; and the pustular type. It is now generally accepted that the acne bacillus is the direct cause of all cases of acne. In the pustular variety of this disease, the staphylococcus is the chief complicating factor. In the vaccine treatment of the non-pustular type of acne, the plain Acne Vaccine is indicated; while the pustular variety is best treated with a combined vaccine containing the staphylococcus as well as the acne bacillus.

Vaccine therapy is not in itself always sufficient to correct this condition. While it is a striking advance over the older methods of treatment, nevertheless it must be combined with proper surgical and medical measures in order to obtain good results. When Acne Vaccine was first used, too large doses were usually given; and the injections were followed by the appearance of new lesions. There is no rule that can be made in regard to dosage which will

apply to all cases. It depends not only upon the nature of the infection, but also on the individual susceptibility. The local reaction following the injection must also be interpreted properly. Marked tenderness with induration and erythema prolonged for several days is an indication of excessive dosage. If new lesions appear within three days after injection of the vaccine, it indicates that the dose was too large.

#### DOSAGE OF ACNE VACCINES

In administering Acne Vaccine, the technic of Engman has proved to be of value. Best results are obtained with initial doses of three million. After three days, the lesions are opened, gently massaged, the larger comedones extracted, and moist hot compresses applied twice daily. On the sixth or seventh day an injection of 3 to 5 million is given, and the same local treatment repeated for three days. After this, the dosage is gradually increased to 10 million. Small doses at intervals of 5 to 7 days have given the best results. In some cases larger doses may be tolerated by the patient and are indicated; but great care must be exercised in giving increased dosage, especially as to the

number and development of new lesions following such an injection.

The initial dose of the combined vaccine should not exceed 5 million of the acne bacilli and 50 million staphylococci. Subsequent doses may be increased as indicated by the clinical symptoms.

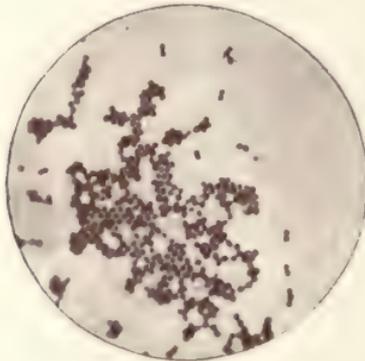
Morris and Doré after extensive use of vaccines in acne do not recommend their use as a routine treatment but prefer to reserve them for carefully selected cases. The cases may be divided into two groups. The first consists of cases characterized by deep-seated pustules situated on the chest, face and back. In such cases, the combined vaccine administered during a period of several months is of some value. The second group comprises cases in which the lesions are superficial and indolent, mostly papules and comedones. In these, Acne Vaccine gives good results in a large proportion of cases. Morris and Doré concludes that: "Experience prevents us from claiming more for vaccine therapy in acne than that it is a useful adjunct to the ordinary forms of treatment."

In the management of every case of acne, general measures—hygienic and dietetic—must be

employed. Marked improvement is brought about by vaccine therapy in a large number of cases and a majority of them are cured. It should be borne in mind, however, that the duration of treatment in the majority of cases extends from 3 to 5 months, while 6 to 12 months or more may be required for the severe types.

### BOILS

In the entire list of disorders due to bacterial infection there is probably none which offers



Staphylococcus.  
× 1,100 diameters.

more evidence in favor of vaccine therapy than furunculosis. It was in this condition that Wright first tried inoculations with staphylococcus vaccine and in which he secured such

favorable results. There are some cases, however, of furunculosis that do not respond readily to vaccine treatment regardless of the nature of the vaccine. Such failures may be due in some instances to error in the size or interval of the inoculations. Boils are almost always caused by the staphylococcus aureus; although some cases are seen in which both the albus and aureus type are present, and some in which the staphylococcus albus alone is found. Therefore, in treating this condition it is best to use a Staphylococcus Vaccine containing both the albus and the aureus variety.

As in other conditions amenable to vaccine therapy, the question of dosage and interval between injections is of the utmost importance in treating furunculosis. Although no set rule can be given in regard to the administration of the vaccine, the best and safest procedure is to begin with a rather small dose—50 to 100 million in adults and about 25 million for children—the injections being given usually at 5-day intervals. Using the local reaction and clinical course of the disease as a guide, the dosage may be increased until 500 to 1,000 million are given to an adult and 100 to 250 million to children.

Frequently, after two or three injections, no new lesions will appear and the pre-existing ones gradually clear up. Three or four inoculations should be made after the disappearance of all lesions. If there should be a recurrence of the furuncles after an interval of several weeks or months, the vaccine should again be given and be continued for a longer period than previously until the disappearance of all lesions. When the vaccine is administered properly, there is much less probability of a recurrence than with any other method of treatment.

#### SYCOSIS VULGARIS

This type of sycosis is usually due to the staphylococcus aureus and is frequently quite resistant to local treatment, owing to the deep-seated character of the infection. Staphylococcus Vaccine should be administered in initial doses of 100 million gradually increased to 500 million or more at intervals of 5 to 7 days.

#### ECZEMA

In certain cases of chronic eczema associated with a pustular infection and more or less weeping, Staphylococcus Vaccines have given favorable results. In the dry scaly type, no benefit

has resulted. Many cases of seborrhoeic eczema where the patients have had eruptions for months or years, according to Gilchrist, have yielded most successfully to *Staphylococcus Albus* Vaccine given in doses of 250 million or more once a week.

### ROSACEA

In rosacea of the erysipelas type, *Staphylococcus Albus* Vaccine will cause the disappearance of the pustules and, as the inflammation subsides, the erythema becomes much less prominent. Gilchrist reported fifty cases with satisfactory results.

### OTHER STAPHYLOCOCCUS INFECTIONS

*Staphylococcus Vaccines* also produce good results in fistulous sinuses, psoas abscesses, suppurating glands and osteomyelitis.

In acute tonsillitis, mastoiditis, puerperal sepsis, etc., a combined vaccine is indicated. Initial doses containing 100 million staphylococci, 25 million streptococci, and 50 million *B. coli* may be given and the subsequent doses increased according to the clinical indications. In abscesses, suppurative periostitis, pleurisy, peritonitis and various pyemic conditions, a

combined vaccine may be administered in initial doses of 100 million staphylococci and 25 million streptococci.

#### ERYSIPELAS

In erysipelas, several workers have noted less frequent recurrences in cases treated with vaccine, but they were unable to see any limitation of the disease. An analysis of the clinical course of 800 cases of erysipelas under the care of Erdman shows that the duration of the disease was not lessened; the mortality remained at the same level, and there was no immunity guaranteed against recurrences. In cases with a minimal degree of constitutional disturbances, vaccines may be used during the attack and as a prophylactic against recurrences; but a successful outcome from the attack cannot be regularly attained.

If vaccine therapy is used in these conditions, it is important to employ a polyvalent vaccine because of the wide diversity of streptococcus strains. The initial dose of Streptococcus Vaccine should be small, 25 to 50 million, the injections being given every second or third day; but, if no improvement follows after 24 hours, another dose may then be given. In erysipelas

and other streptococcic infections, exhibiting extreme intoxication with lowered vitality of the patient, Antistreptococcus Serum given intravenously or subcutaneously will induce more rapid and favorable results than vaccine therapy.

## Chapter XXII

### GENITO-URINARY INFECTIONS

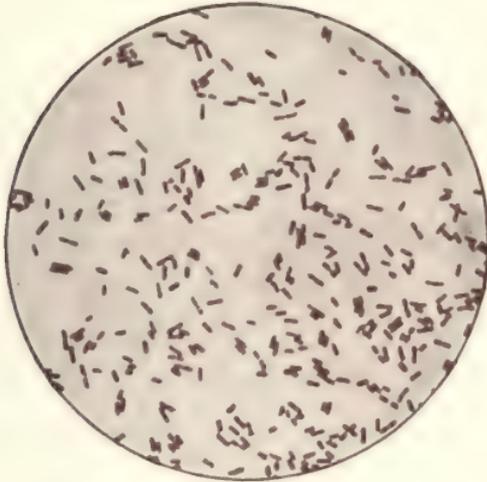
The colon bacillus is the direct or complicating cause of numerous infections of the genito-urinary tract and rectal region including cystitis, pyelitis, rectal abscesses, fistula-in-ano, sinuses, etc. Colon Vaccine is employed alone or in combination with other vaccines in the treatment of these infections. A small initial dose is advised after which the amount may be rapidly increased. From 5 to 50 million may be given for an initial dose, the injections being given every 3 to 4 days; but later in the disease, intervals of ten days are used.

### GONOCOCCUS INFECTIONS

The estimation of the value of Gonococcus Vaccines depends largely on the viewpoint of the individual user and the kind of cases in which the vaccine is employed. Treatment of gonococcus infections may be conveniently considered first, from the point of the original infection of the mucous membranes; and second,

the treatment of the complications which include local extensions—such as tubal infections, epididymitis, arthritis, etc.

*Urethritis*—There have been a few reports of beneficial results in the treatment of gonorrhoeal



*Bacillus coli communis* (Colon bacillus).  
Twenty-four-hour agar culture.

urethritis by *Gonococcus Vaccines*, but the majority of workers who have had wide experience agree that vaccines produce little if any demonstrable effect in shortening the course of the disease. In old cases, a temporary in-

crease in discharge has been noted after the use of vaccines, and this procedure has been suggested as a method of determining the cure of such cases. Active immunization in gonorrhoea has also been suggested as a means of preventing complications, by increasing immunity and thus anticipating the possible spread of the infection from the primary focus. Other bacteria, such as the staphylococcus and colon bacillus, undoubtedly play a large part in the continuance of the urethral discharge; as also do the mechanical difficulties, such as strictures, which develop as a result of prolonged inflammation.

*Vulvovaginitis*—Some observers believe that the course of vulvovaginitis in children has been shortened by the use of vaccines; others that the methods have been of no demonstrable value. It would appear that, while treatment by vaccines has not been clearly shown to shorten the period of treatment, they may be cautiously used in combination with other approved local procedures.

*Ophthalmia*—A limited number of cases of ophthalmia treated by vaccines have been reported, but the results do not appear better than infections of other mucous membranes. The col-

lected reports on the treatment of gonococcus infections of the mucous membranes by vaccines present no clear evidence of their efficacy. As a prophylactic against metastatic complications, they may have some value.

*Iritis*—Certain cases of iritis of the recurrent type have apparently received benefit from Gonococcus Vaccines. When intelligently employed under the supervision of a competent ophthalmologist, this method offers some hope of benefit in a condition not readily amenable to other treatment.

*Arthritis*—In summarizing the results reported by a large number of writers in America, Germany and England, Bruck states: "The favorable influence of Gonococcus Vaccines in the active treatment of complications of gonorrhea: arthritis, epididymitis and infections of the adnexae, has been emphasized by those who have concerned themselves with the subject".

The general impression seems to be that the course of gonorrhoeal arthritis is favorably influenced by inoculations of Gonococcus Vaccines. Kutner and Schwenck conclude that cases of arthritis are benefited by vaccines.

Frost obtained favorable results in arthritis and epididymitis with polyvalent vaccines. Baetz treated 28 cases of gonorrhoeal arthritis in the Canal Zone. He concludes that vaccine treatment gave very good, sometimes brilliant, results in the majority of cases. Unfavorable results due to treatment were not noticed. The average number of days' treatment per patient was twenty-four.

The most favorable cases are those in which lesions are subacute, and in which secondary anatomic changes are limited. It should be obvious that in cases of long standing with disorganization of joint structure, all that can be obtained by specific measures is the prevention of new infections; and, that the repair of the joints, if at all possible, must come from other agencies. Schultz saw prompt improvement in 11 out of 16 cases of arthritis and concludes that the treatment is specific, as shown by focal, local and general reactions; and cases reacting with fever do better than those which show no reaction.

*Epididymitis*—Many series of cases of epididymitis are on record in which vaccines are credited with hastening the cure. Klause has

reported the results of treatment of 700 cases by *Gonococcus Vaccines*. Cases of recent epididymitis promptly healed after two or three inoculations. Cases of arthritis were also benefited by vaccines. Urethritis and prostatitis treated by vaccine showed no improvement greater than could be obtained by other methods.

*Pelvic Infections*—The action of *Gonococcus Vaccines* in pelvic infections of women has been described by Hauser, who believes that in recent cases *Gonococcus Vaccines* have a specific curative value, and further, that inoculations must be carefully conducted to avoid doing harm. The value of *Gonococcus Vaccines* in gonococcal pelvic lesions is not clearly determined. If vaccines are employed, care should be taken that the dosage is not excessive. A number of reports on the use of *Gonococcus Vaccines* are available in which there is an expressed belief that the improvement was more rapid than in control cases not inoculated.

In general, it may be said that *Gonococcus Vaccine* is of value chiefly in the treatment of gonorrhoeal arthritis, vulvovaginitis of children, salpingitis and, to a variable degree, in acute urethritis. In subacute urethritis, chronic pos-

terior urethritis (gleet), epididymitis, and gonorrhoeal rheumatism, a combined vaccine containing the gonococcus, staphylococcus, streptococcus and *B. coli* is usually required in order to combat the mixed infection.

#### DOSAGE OF GONOCOCCUS VACCINES

The dosage recommended in gonococcus infections varies greatly—from one million to 1,000 million being advised by different workers. From 5 to 50 million is a good initial dose, which may be increased up to 1200 million or more. A combined vaccine is used in initial doses of 75 million gonococci, 50 million *B. coli*, 75 million streptococci and 300 million staphylococci, until 15 or 20 times these amounts are given. The intervals between the doses vary from two to seven days.

#### REACTION

The degree of reaction allowable must be determined by a study of the individual case, but in general it is safe to restrict the dosage so that the clinical changes in the patient immediately following the inoculation are relatively slight. In the treatment of arthritis and epididymitis. Bruck believes that a slight temperature reac-

tion of one to two degrees is indicative of the efficiency of the dose.

#### LOCAL MEASURES

In acute gonorrhoeal urethritis, local treatment should be employed in conjunction with vaccine therapy, because bacteria will continue to develop on the surface where phagocytosis cannot readily take place.

In the complications following a primary gonococcus infection, especially if a profound toxemia exists, Antigonococcus Serum administered intravenously or subcutaneously will be productive of more rapid and favorable results than vaccine treatment.

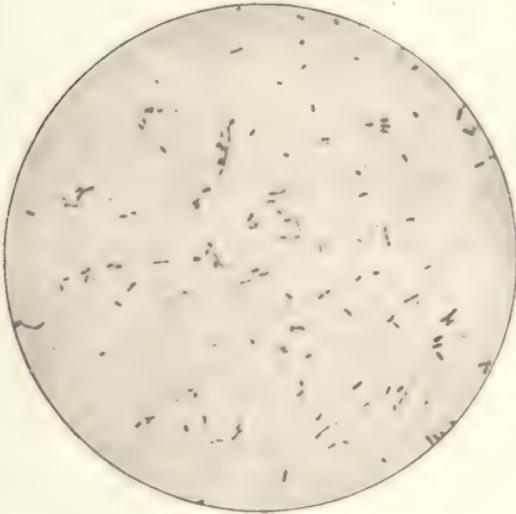
## Chapter XXIII

### DISEASES OF THE RESPIRATORY TRACT

#### COLDS AND INFLUENZA

Colds, whether acute or chronic, are due to bacterial infection. The bacteria commonly found in the respiratory passages of healthy persons are the pneumococcus, staphylococcus, streptococcus, influenza bacillus, and members of the micrococcus catarrhalis group. When the mucous membrane is in a weakened condition—owing to undue exposure of the body to sudden changes in temperature—the local vasomotor disturbances increase the secretions and the bacteria grow more rapidly and may become sufficiently virulent to attack the tissues. Exposure and other predisposing causes are not always required to produce an acute or chronic cold, for sometimes the bacteria in the respiratory passages become sufficiently virulent to attack a perfectly healthy person, and contagious colds spread in the same way as an epidemic of measles or scarlet fever.

Recovery from colds follows in the same way as recovery from other infectious diseases: antibodies are formed, which destroy the attacking bacteria. These antibodies are specific for each



*Bacillus influenzae*.  $\times 1,100$  diameters.

microorganism concerned—that is, if antibodies for the pneumococcus alone are produced in sufficient quantities to destroy that microorganism, the other bacteria present may still be able to continue the infectious process. Hence, before recovery can take place, specific antibodies

must be formed to destroy all the types of bacteria involved.

*Bacteriology*—Bacteriologic examinations of diseases of the nose and respiratory tract by Birkett, Meakins, Patterson (*The Laryngoscope*, September, 1910), and other investigators have demonstrated that no one specific microörganism is always present as the causative agent, but rather several bacteria. The most commonly found bacteria are the micrococcus catarrhalis, influenza bacillus, Friedlander bacillus, pneumococcus, streptococcus and staphylococcus.

Based on these findings, the vaccine used in the prophylaxis and treatment of colds and influenza must consist of a combination of all of the causative microörganisms. Immunization against these diseases has proved of value, but it is important to correct local pathologic conditions, such as obstructions of various kinds and malformations—polyps, exostoses, adenoids, etc. Immunization is useful in the spring and fall for persons who are subject to repeated attacks of common colds, influenza, and other catarrhal conditions of the nose, throat and respiratory tract.

*Vaccine Treatment*—In treating or immunizing against coryza or common colds of non-epidemic variety, a combined vaccine containing the micrococcus catarrhalis, Friedlander bacillus, pneumococcus, streptococcus and staphylococcus will best fulfill the indications. If the clinical symptoms or bacteriologic examination point to true influenza or “La Grippe” of the epidemic form, the combined vaccine should contain, in addition to the above-named organisms, the influenza bacillus. The clinical results of the use of such combined vaccines have been favorably reported (Stevenson: *Indiana State Medical Association Journal*, June, 1913). One characteristic feature of the vaccine treatment is a general improvement that is induced before the local infection shows much change.

*Dosage*—*For prophylaxis*, four doses are given at 3-day intervals. The initial dose should not exceed 25 million of each variety of bacteria mentioned above, and the subsequent doses may consist of multiples of the first dose. *For treatment*, the initial dose, containing 25 million of each variety of bacteria, is usually followed on the second day by double that dose; and the dosage may then be increased every 3 or 5 days ac-

according to indications, until all symptoms of the disease have disappeared. If marked local or constitutional reaction follows any dose, the subsequent dose should not be increased.

### PNEUMONIA

The pioneer in the work of using Pneumococcus Vaccine was McDonald, who produced artificial crises in rabbits by inoculating them with a vaccine after they had been infected with the pneumococcus. He was able to produce a crisis and recovery at will, and the control rabbits on whom the vaccine was not used died. Harris states that Pneumococcus Vaccine in the sequelae of pneumonia and other pneumococcus infections is as sure as Staphylococcus Vaccine in boils. According to Leary, the crisis in pneumonia under vaccine treatment occurs earlier, the course of the disease is favorably influenced, and there is marked relief from the toxic symptoms. Vaccines are of value in delayed resolution of the consolidated lung in which there is but little remnant of the original general infection.

*Results of Vaccine Treatment*—The effect of the initial dose should be watched to decide the

time of repetition. If the temperature rises from one to three degrees, it will be safest to give no more vaccine during 24 hours. In America, Stoner has reviewed the results obtained in 155 cases of pneumonia treated by means of Pneumococcus Vaccine, with a mortality of 13 per cent. Inasmuch as the average mortality statistics in pneumonia range from 20 to 25 per cent, these figures indicate a marked reduction in the death rate.

In the more chronic forms of pneumococcus infection of the lungs, such as delayed resolution and empyema, it would seem from the experience of Wright that a combined vaccine should be used.

*Clinical Reports*—In the treatment of pneumonia, it is essential that the vaccine be administered early in the disease. Improvement usually occurs within 24 hours after the first injection: the crisis occurs earlier and the duration of the disease is lessened under the vaccine treatment. Major Bispham of the United States Army reported 19 cases of pneumonia, six of which were treated symptomatically with two deaths, while the remaining 13 cases were treated with Pneumococcus Vaccine with no

deaths. He reports (*Military Surgeon*, June, 1913) that the fall of temperature—often of two or three degrees—after injection of the vaccine, together with the great relief from the distressing symptoms, such as pain and dyspnea, was very marked.

*Dosage*—The dosage is regulated on a sliding scale. In most cases an injection of 50 million is sufficient as an initial dose. All subsequent doses should be increased rapidly, giving 100 million on the second day, 200 million on the third day, etc., being guided by the clinical symptoms, including the temperature, physical signs and general condition of the patient. If the patient improves on the day following the primary injection, no vaccine is necessary on that day; but if the temperature remains high, an increased dose may be given at this time.

Most cases of broncho-pneumonia are due to mixed infection, the streptococcus and staphylococcus being present as well as the pneumococcus. Good results in these cases have been obtained by using a combined vaccine, the average initial dose containing 50 million pneumococci, 25 million streptococci and 50 million staphylococci, repeated daily until the tempera-

ture becomes normal and then continued at intervals of 3 to 5 days to prevent relapse.

*Prophylaxis*—The prophylactic use of Pneumococcus Vaccine has been given a decided impetus by the series of experiments carried out by Sir A. E. Wright. In recent years, there has arisen in South Africa among the natives employed in the mining district, a severe type of pneumonia with a high death rate. In attempting to combat this condition, Wright has had the opportunity to test on a very large scale the value of prophylactic Pneumococcus Vaccine. After considerable experimentation, the administration of a single large dose containing 1,000 million bacteria was found to be the best way in which to give the vaccine. In his report, Wright thinks that the prophylactic vaccine was effective in reducing the incidence of pneumonia among the natives during the first three months following inoculation.

In the treatment of pneumonia, especially cases exhibiting extreme intoxication with lowered vitality of the patient, Antipneumococcus Serum given intravenously or subcutaneously will induce more rapid and favorable results than vaccine therapy.

## WHOOPING-COUGH

Probably no disease which affects the human subject, and particularly children, has so consistently baffled the efforts of physicians to successfully treat it as has whooping-cough. The entire gamut of the pharmacopeia has been run in an effort to discover a drug which would produce some consistent results, but to no avail. Not until it was demonstrated that a specific microorganism caused the disease was there any hope of solving the perplexing problem of treating whooping-cough. Early in the course of the disease, the Bordet bacillus is present in large numbers; but after the first week, it is associated with the influenza bacillus, the pneumococcus and other bacteria, the presence of which favor the development of broncho-pneumonia which so frequently causes a fatal termination of this widespread disease.

*Vaccine Therapy*—The most recent, effective and rational method of treating whooping-cough is by means of a combined vaccine. Dr. E. Mather Sill of the New York Polyclinic Hospital and Medical School (*American Journal of Diseases of Children*, May 1913, and *American Medicine*, June 1913) has used this method of

treatment almost exclusively for several years; and, up to the present time, has treated 61 patients with better results than he had previously obtained by means of drugs (*Forchheimer's Therapeutics*, 1914, v, 302). The youngest child treated was one month old and the oldest ten years of age. The combined vaccine diminishes the severity and number of the paroxysms and the amount of vomiting, and shortens the course of the disease. No harmful effects have been noted; freedom from complications being one of the favorable effects of the treatment.

In the series reported by Dr. Sill, the average length of time that his patients coughed after being placed on vaccine treatment, was 3½ weeks; and other clinicians have reported equally good results. This is an important practical result, for the usual uncomplicated case of whooping-cough runs from 9 to 12 weeks, and the more severe ones last a considerably longer time. Usually, according to Sill, after two or three injections of the vaccine, the number and severity of the paroxysms and the vomiting is decidedly lessened; and the child is able to retain its food, and rapid improvement follows.

*Dosage*—In treating whooping-cough, the

combined vaccine is usually given every second day, but some clinicians now advise, especially in severe cases, that the doses be administered daily. The practitioner must be guided mainly by the number and severity of the paroxysms in giving the vaccine. It is recommended that the combined vaccine be given every two or three days in doses containing from  $12\frac{1}{2}$  million to 100 million each of the Bordet bacillus, influenza bacillus, pneumococcus, streptococcus and staphylococcus, according to the age of the child and the severity of the disease. It is advisable, especially in babies and young children, to administer a small initial dose containing  $12\frac{1}{2}$  million of each of the above-named bacteria, and this dose may be gradually or rapidly increased as symptoms may indicate. According to the published reports, it seems perfectly safe to give an initial dose of 25 million of each of the foregoing bacteria to a child over two years of age, subsequent doses being made larger according to the requirements of the individual case.

Clinical results seem to indicate that the vaccine given in fairly large or ascending doses brings about a more rapid cure than smaller doses of constant size. The duration of whoop-

ing-cough is less than half what it was when treated with drugs. Vomiting, which is usually such an annoying and serious symptom of whooping-cough on account of its exhausting effect, is often quickly relieved by means of the vaccine. Complications which have been so common under the older methods of treatment have been of rare occurrence under vaccine treatment. The data that have already been accumulated by numerous workers indicate that the combined vaccine has a distinct value in the treatment of whooping-cough, particularly in the alleviation of symptoms and in shortening the course of the disease.

#### PYORRHEA ALVEOLARIS

Pyorrhæa alveolaris is a purulent inflammation of the dental periosteum, with progressive necrosis of the alveoli and loosening of the teeth. The causative factor of pyorrhæa alveolaris is still a mooted question but the work of Bass and Johns (*The Journal A. M. A.*, Feb. 13, 1915, p. 553) indicates that an endameba is present. Bacteriologic investigation reveals the constant presence of the streptococcus or the pneumococcus in pyorrhæal infections. At times, other

bacteria are associated, such as the staphylococcus and micrococcus catarrhalis, as shown by Ross of Toronto (*American Medicine*, May, 1914) who has recently reviewed the subject very comprehensively. When combined with the proper local treatment, vaccine therapy may be a valuable aid in treating this condition. A combined vaccine containing 50 million pneumococci, 25 million streptococci and 50 million staphylococci as an initial dose may be given; subsequent doses being administered at intervals of five to seven days.

#### OTITIS MEDIA

Inoculation of vaccines in chronic suppurating processes of the ear and of the accessory sinuses of the head has been extensively practised. Before vaccine treatment is instituted in any case, the physician should make sure that the persistence of the purulent discharge is not due to mechanical causes, such as inefficient drainage, retained secretion, or polypi.

Acute otitis media is not only a very painful disorder, but it often leads to deafness; and, not infrequently, the infection extends into the mastoid cells, resulting in mastoiditis. The impor-

tance of bringing this infective process rapidly under control with vaccine treatment can be readily appreciated. The important pathogenic bacteria usually found in acute otitis media are the streptococcus, staphylococcus and, at times, the pneumococcus. In treating this condition, a combined vaccine containing these microorganisms is being extensively employed by many otologists. The initial dose of this vaccine contains 50 million pneumococci, 25 million streptococci and 50 million staphylococci; subsequent doses, containing multiples of this dose, are given at 3 to 5-day intervals according to clinical indications. If the vaccine is given early, the ear-drum may often be saved; but if there is much bulging of the drum, it should be lanced. Where the ear-drum is punctured, it will be found that the discharge will often dry up in much less time if a vaccine is used.

Bacterial examinations of the pus in the early stages of suppurative otitis media show that, in a large majority of cases, the streptococcus is the primary infecting microorganism. After rupture of the ear-drum, contamination soon takes place and staphylococci are found and, at times, the bacillus pyocyaneus. In treating

these cases, therefore, a combined vaccine containing the staphylococcus and streptococcus will be found to be a valuable means of hastening recovery.

## Chapter XXIV

### ACUTE GENERAL INFECTIONS

#### TYPHOID FEVER

The most complete analysis of the bacterial therapy of typhoid fever has been made by Watters (*Medical Record*, 1913, LXXXIV, 518) who has summarized the results obtained in the treatment of 1,120 cases, of which 158 had been treated by himself during the past six years. The mortality was 4.7 per cent. He states that during a similar period of observation in 100 patients with typhoid not receiving vaccines, there was a mortality of 13 per cent. It appears from Watters' series that (1) the mortality was slightly lower among the patients treated by vaccine than among those who did not receive such treatment; (2) the duration of fever was about ten days less in the vaccine-treated cases; and (3) the percentage of relapses was diminished in the vaccine-treated cases.

*Mortality Lowered by Vaccines*—Callison (*Medical Record*, June 24, 1911, page 1129) collected 323 cases in which this disease was treat-

ed with vaccines. There was a mortality of 4.6 per cent. He concludes: (1) Inoculations of vaccine in typhoid fever prevent relapses and lessen complications and, in some cases, probably shorten the original attack. (2) In therapeutic doses, such vaccines are without injurious effect and do not interfere with other treatment.

*Dosage*—It has been estimated that the number of cases of typhoid fever in the United States is now about 150,000 annually and the deaths approximately 25,000, or 16.5 per cent. Hence, the mortality reported by Watters and by Callison is a decrease of three-fourths of the usual mortality.

The dosage of the vaccine varies considerably with different observers. For example, Semple used doses of 50 to 200 million; Smallman used doses of 100 to 300 million; Hollis used doses of 10 to 250 million; Callison used initial doses of 100 to 300 million and recommended that subsequent doses be increased by 100 million; and Meakins and Foster used doses of 1,000 to 2,000 million. Most of these authors have felt convinced that patients treated with vaccine suffered less depression, had lower temperatures,

were brighter and had fewer complications; and that, conservatively used, vaccines can do no harm in the treatment of the disease.

### SCARLET FEVER

It has been shown that much of the severity of this disease and practically all of the sequelae are due to the streptococcus. In view of the remarkable results obtained in Russia by the use of *Streptococcus Vaccine* for the prophylaxis of this disease, it has been recommended that the vaccine be used in the treatment of the disease in order to combat the complications and lessen the severity of the disease. For this purpose *Streptococcus Vaccine*, prepared from strains isolated from scarlet fever cases, may be given in initial doses of 25 to 50 million gradually increased according to the clinical indications.

In the treatment of scarlet fever, particularly those cases which exhibit extreme intoxication, the administration of *Antistreptococcus Serum* intravenously or subcutaneously will induce more rapid and favorable results than vaccine therapy.

### RHEUMATISM

The specific causative agent of acute articular

rheumatism has not yet been definitely proven; but extensive research by numerous investigators has demonstrated the presence of streptococci or pneumococci in the joint fluid. Favorable results are being reported from the use of a combined vaccine in articular rheumatism. The initial dose of such a combined vaccine contains 100 million streptococci and 50 million pneumococci; subsequent doses being increased according to clinical symptoms. The subsidence of pain is the first symptom of relief, followed by lessened inflammation of the joints. A very important feature of the vaccine treatment of articular rheumatism is that it materially reduces the number of heart complications which so commonly follow this disease.

For information concerning the use of bacterial vaccines in the treatment of gonorrhoeal rheumatism, see arthritis under gonococcus infections on page 269.

## Part VI

### CULTURE PRODUCTS

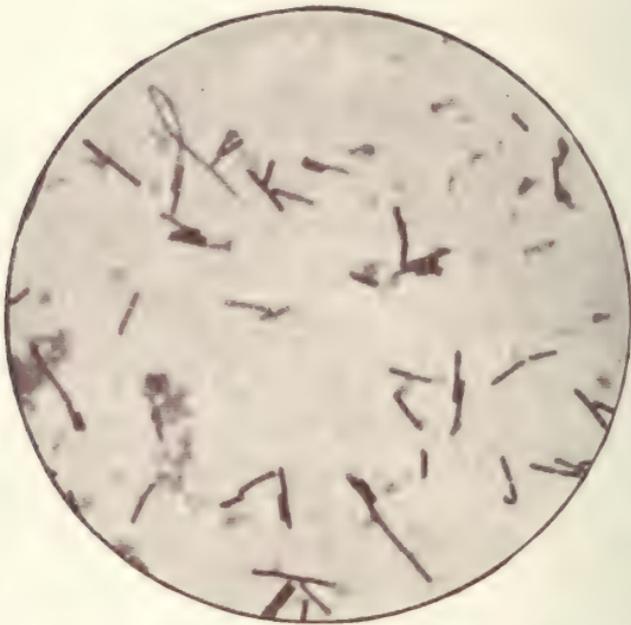
#### Chapter XXV

#### CULTURE OF THE BACILLUS BULGARICUS

*Historic*—Among the various lactic acid-producing bacteria, it was found by Metchnikoff that the bacillus bulgaricus, isolated in Massol's laboratory at Geneva, exerts an antagonistic action against the growth of putrefactive bacteria by the large amount of acid which it produces. Metchnikoff further discovered that the bacteria which cause putrefaction will not live in the presence of the bacillus bulgaricus, which, he found, is the only lactic acid bacillus known that will survive ingestion, reach the large intestine and continue to live there, creating lactic acid and displacing the putrefactive bacteria.

*Action*—The therapeutic value of a culture of

the bacillus bulgaricus is dependent upon the power of the bacillus to live in the intestine and there produce lactic acid, the presence of which is unfavorable to the growth of putrefactive



Bacillus bulgaricus.  $\times 1,000$  diameters.

bacteria which thrive best in an alkaline medium.

*Indications*—The culture of the bacillus bulgaricus is indicated in the treatment of intes-

tinal toxemias due to deficient gastric digestion, abnormal alkaline putrefaction, indicanuria, chronic constipation of children, toxic diarrheas of infants, mucous colitis, typhoid fever, rheumatic conditions, and arteriosclerosis.

The culture has also been applied locally with some degree of success in the treatment of suppurative conditions, such as otitis media, ozena, atrophic rhinitis, etc.

*Diet*—Sugar in some form is necessary to secure proper growth of the bacillus bulgaricus. Hence, in order to produce lactic acid, it is necessary to have carbohydrates present in the intestine to supply food for this bacillus. Prunes, beets and carrots are especially recommended as part of the diet. The use of such carbohydrate foods, with only a moderate amount of protein (meats), and the elimination of red meats from the diet, will aid the acclimation of the bacillus bulgaricus within the intestine and thus inhibit putrefactive changes in the intestinal tract.

*Dosage*—In the treatment of infantile diarrhea and intestinal toxemias of adults, 5 to 15 c.c. or more of the culture may be given in a little sweetened water or milk, every 2 or 3

hours, until improvement occurs. Then the same dosage should be administered 3 or 4 times daily, before food, until all toxic symptoms have disappeared.

## Chapter XXVI

### LOEFFLER'S BLOOD-SERUM CULTURE MEDIUM

It is universally conceded by bacteriologists that blood-serum in the form of Loeffler's mixture is the most favorable medium for the growth of the diphtheria bacillus. On this medium, diphtheria bacilli grow very rapidly and are not easily overgrown and obscured by contaminating bacteria. Therefore, Loeffler's Culture Medium is used particularly for diagnostic purposes in examining cultures from the nose and throat of persons suspected of having diphtheria.

According to Mallory and Wright, the blood-serum mixture of Loeffler is the best culture medium for the routine examination of pathologic material. Owing to the more rapid and luxuriant growth of certain important pathogenic bacteria upon it than upon ordinary media, Loeffler's Blood-Serum Culture Medium is adaptable for a large variety of diagnostic work.



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