INFECTION AND IMMUNITY—A REVIEW.

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1. CONDITIONS OF INFECTION. Infection is the successful invasion of the body by living parasites. The broader sense of the term, however, conveys to our minds, not only the process of invasion and multiplication of the micro-organisms, but also the results of their specific functions upon the tissues of the body, the pathological process. Infection, therefore, results from the entrance into the body of living, pathogenic micro-organisms, and its symptoms or manifestations depend upon influences relative to invading micro-organisms as well as the body which they invade. Anything modifying either the micro-organisms or the host must necessarily have its effect upon the final result. There are, therefore, many conditions, some of which are recognized, that control, to a certain extent, infectious or diseased processes.

Infecting Agent. The conditions which modify infection, as regards the infecting agent, are *virulence*, the *number of micro-organisms gaining entrance to the body* and the *mode of entrance.*

Virulence may be defined as the power of micro-organisms to multiply within the body and produce disease. If the virulence is increased, if in some way the power of a certain micro-organism to produce a specific disease is intensified, then the dose or the number of invading micro-organisms need not necessarily be so large to produce a like infection. We have, at present, very little knowledge of Nature's way of modifying the power of micro-organisms to produce disease, although in the laboratory, under experimental conditions, we may increase and decrease their virulence by several methods. The most common methods of increasing the virulence, are by passing a pure culture of a pathogenic micro-organism through an animal, growing the organisms upon culture media containing unheated body fluids, such as blood, serum or ascitic fluid, or in a collodion sac within the body cavity of an animal. The value of these methods depends upon the fact that the micro-organisms, while developing, come in contact with some of the properties derived from the living animal, and, therefore, approach Nature as closely as possible. The virulence of the virus of rabies is increased by passing it successively through rabbits, as is also the case of many known bacteria, as the pneumococcus, streptococcus and others. The virulence of the glanders bacillus, the diphtheria bacterium and other micro-organisms are strengthened by passage through guinea pigs. On the other hand, the virulence of micro-organisms may be decreased by removing them from their natural environment and regular source of food supply and growing them on artificial culture media. It is found, as a rule, that under these conditions the growth of the micro-organisms will gradually become more luxuriant at the expense of their virulence.

There are occasions, however, when the virulence of an organism or virus is decreased on passing through an animal. While the virus of rabies will increase on passing through rabbits, it decreases on being passed through monkeys. This is well illustrated by the smallpox virus, which presumably decreases its virulence by passing through a heifer, and we have as a result a much milder infection. We cannot state this as an absolute fact, as the nature of the virus of smallpox or cowpox is unknown. By making use of the cowpox virus, or the smallpox virus in its altered state, we have a means of protecting against the disease in its natural state, as the smallpox vaccine will immunize against either smallpox or cowpox.

Under ordinary conditions, given the dose large enough, and the organisms virulent enough, to produce a specific infection, the results will depend, in a large part, on the path taken by the invading micro-organisms. The portals of entry, or the paths by which micro-organisms gain entrance to the body, are the broken skin, the digestive tract, the respiratory tract, the genital tract and the conjunctiva. Many of the causal organisms of the acute infections are very selective in their methods, producing their specific diseases only when allowed to enter the body by certain paths. The typhoid bacillus as well as the cholera spirillum have chosen the alimentary tract as their portal of entry, and will infect the individual in no other way. The gonococcus elects the urogenital mucous membrane, or the conjunctiva, and there is no evidence at hand to prove that specific symptoms may be produced through the skin, alimentary tract or respiratory tract. The tetanus bacillus produces its deadly results through the broken skin or mucous membrane, while the diphtheria bacterium prefers the mucous membranes of the pharynx, and is seldom found in any other situation.

Subject of Infection. Pathologic bacteria are rather underhanded in their methods of warfare for, although they are ever present, they rarely attack the body unless its natural defenses and protections are disabled or broken down; or, as we say, the resistance is lowered and the individual is susceptible. In this case, the normal equilibrium being in some way disturbed, the dormant but virulent micro-organisms, taking advantage of the situation and rapidly increasing in number, produce the infection. Susceptibility or lowered resistance, or in other words, imperfect or impaired reactive powers, are, as a rule, brought about by one or more of the following conditions: fatigue, exposure to cold, heat or dampness, poor hygiene, noxious gases, drugs, trauma and operation, other diseases, improper diet, thirst and age. How these various conditions affect the normal defenses of the body we are at a loss to explain.

2. VARIETIES OF INFECTION. The results of the growth of pathologic bacteria within the body manifest themselves in an infinite variety of ways. After the micro-organisms gain entrance to the body, they may remain at or near the point of entrance, or may find their way—by means of the blood stream, lymph channels or contiguous tissues—to some remote spot; in either situation they may multiply and produce an infection. This form of infection is termed local, and may be either acute or chronic, depending upon the length of time the morbid process has continued. Cerebrospinal meningitis, diphtheria, tetanus, the early manifestations of gonorrheal infection, as well as the ordinary pus infections, are typical local infections.

A general infection, on the other hand, is one in which the micro-organisms are found disseminated throughout the entire system. This is termed a bacteremia or a septicemia. Typhoid fever and pneumonia are typical general infections. The primary focus of the infection is to a certain extent localized (in the lungs in pneumonia and in the intestines in typhoid), but the bacteria may be isolated, in the majority of cases, from many of the internal organs as well as from the blood stream. This condition must be distinguished from that of diphtheria and tetanus (the toxemias), in which case, although the infection is localized, the toxins and not the bacteria are found diffused throughout the system, the symptoms resulting from the action of these toxins alone. It is impossible to draw a sharp line between the local and general infections, or the bacteremias and toxemias, for in many of the local infections blood cultures may show the casual organism in the circulating blood stream, and in all infections, both local and general, there is always some general intoxication produced.

A primary infection is an original or initial infection, which is often followed by a secondary. It is, as a rule, the principal infectious process, invading the body at one time, although it may prove not to be the one to cause the death of the individual.

A secondary infection is a condition found when some other infectious process is implanted upon or associated with a primary infection. Secondary infections are usually caused by the pus organisms. When the susceptibility of the body, due to its lowered resistance, following the primary infection, is increased, the secondary organisms, which may have been present in the normal body in a quiescent state, begin to multiply, and cause symptoms typical to themselves.

Mixed or concurrent infections occur when two or more different bacterial species are found associated. Acute rhinitis, an ordinary "cold in the head," as it usually manifests itself, is a typical example of a mixed infection.

Terminal infections are found in the chronic organic diseases; as, heart disease and Bright's disease. In such cases, one or more pathogenic micro-organisms gain entrance to the body, and, encountering no resistance, due to the already decreased vitality of the body, multiply with great rapidity and produce death within a short time. The primary disease might have resulted fatally in time, but it is the secondary infection which terminates the case. Pneumonia is one of the most frequent terminal infections. The terms "mixed" and "secondary," or "secondary" and "terminal" are often used interchangeably, for there is no hard and fast line of distinction between them, except that a terminal infection always results in death.

3. MODES OF BACTERIAL ACTION. It is generally believed that in all infections the chief symptoms are due to the injurious nature of the products formed by the bacteria, and not to the invasion of the bacteria alone. In many cases, however, the intoxication is absolutely dependent upon the invasive power of the micro-organisms, and unless this is strong enough to overcome the resistance of the body, infection will not result. On account of the poisonous nature of these products they are termed toxins. These toxins are presumably of two classes, the extracellular or exotoxins (diphtheria, tetanus), and the intracellular or endotoxins (typhoid, pneumonia and others). A few bacteria, such as the tetanus bacillus and the diphtheria bacterium, with very limited invasive powers, eliminate highly active specific toxins, which produce typical symptoms of the disease, even when separated from the bacteria. These toxins may be found in solution

in the liquid culture media containing the growing micro-organisms, or in the body, after being formed by the bacteria; in which case they enter the circulation and act upon parts of the body remote from the bacteria themselves. The symptoms of the diseases are due to the toxins. Unlike ordinary chemical substances, most of the true toxins act only after a definite length of time, or incubation period. Other varieties of micro-organisms, with invasive powers less limited than the former, may be found growing in some localized area, but exciting actively destructive reactions in the tissues with which they come in contact. These are the staphylococci, streptococci, gonococci, meningococci, and others. Still another variety may be found either in a limited invasion, or in a general infection where the severe symptoms are also due to toxins, as in pneumonia, typhoid fever, and cholera. Lastly, we have a variety of micro-organisms that depend entirely upon the general invasion before the toxin can produce the injurious symptoms, as with the anthrax bacillus. The toxins, however, in all of the last three varieties are endotoxins. They are not found in the culture media in which the organisms grow, are isolated with difficulty from the micro-organisms, and then only after their death, and do not produce symptoms of the specific disease if injected subcutaneously or otherwise, although they may produce severe symptoms and even death. The toxic power of these bacteria is intrinsic, and is dependent in great part upon their invasion.

4. NATURAL DEFENSES OF THE BODY AGAINST THE INVASION OF MICRO-ORGANISMS. Nature, with its unlimited resources, has endowed the human body with many wonderful and varied devices and means for defending and protecting itself against the invasion of micro-organisms, and for neutralizing the deadly poisons as they are formed during the growth of these bacteria within the body.

The External Defenses. For preventing the bacteria from entering the body we have the skin and mucous membranes. On those parts most exposed to injury, such as the soles of the feet and palms of the hands, we find the epidermis or cuticle much thicker and tougher than in other parts. The bacteria gain entrance through these parts only by means of an injury to them. For those parts of the body that are not so much exposed to external influences, and, on account of their situation it is necessary that their surfaces rub together continually, nature has provided a lubricant to prevent them from erosion. The lubricants are the products of the secretions from the salivary, the gastric, the lacrimal, the mucous, and the serous glands. Aside from the protection afforded by the lubrication of the surfaces, as well as an aid in washing away the bacteria, these fluids have, to a certain extent, germicidal or at least antiseptic properties. Under normal conditions, the pathogenic micro-organisms, if not killed, are checked in their growth, and often prevented from multiplying and producing disease. We are still in the dark as to the nature of these antiseptic properties. We do know, however, that although we are unable to use any of the ordinary disinfectants on these surfaces, operations upon the eye, mouth, stomach or anus are rarely followed by infection due to entrance of bacteria at the field of operation. The respiratory tract, which is constantly invaded by foreign particles, as dust, coal and other debris, carrying many hundreds of bacteria with them, is protected, not only by the mucous of the lining membrane, but also by little hair-like processes called cilia. These are continually moving in one direction, making it possible for any foreign particles, which may lodge upon the surfaces, to be gradually swept away from the lungs toward the exterior of the body.

The Internal Defenses. A study of the internal defenses of the body brings us at once to the subject of immunity. Immunity is that condition of the body whereby it resists the development of infectious or morbid processes. The external defenses oppose the entrance and retard the invasion of micro-organisms; while the internal defenses resist their development, or protect the body tissues against their poisonous products, if, by chance, the micro-organisms manage to find their way past the external defenses. As we are dealing with the products of bacteria (toxins) as well as the bacteria themselves, we must distinguish between an antimicrobic and an antitoxic immunity. One is an immunity to an infection, while the other is an immunity to an intoxication. An individual may possess an immunity to a certain micro-organism or to its toxin, or both, but the possession of one property does not necessarily imply the possession of the other. The inoculation of an animal with a large number of Bacterium diphtheriæ will not necessarily cause the appearance of unfavorable symptoms, although the injection of a very small quantity of toxin eliminated by the same strain of organisms invariably means death. On the other hand, an animal might be immunized against the endotoxin of a virulent strain of an organism such as the pneumococcus, and at the same time succumb to the injection of a small number of the live organisms.

From an early period in the history of immunity, there has been a tendency for investigators to be divided into two schools relative to the methods pursued by the body in protecting itself against the ravages of pathogenic micro-organisms; one dominated by the idea that the body fluids are chiefly concerned (the "humoral" view), the chief supporter of which is Ehrlich; the other, championed by Metchnikoff, attributing the most important role to certain cells of the body (the cellular view). More recent work has shown that these views are not necessarily antagonistic, but that both seem to have their part to play in the study of the processes of immunity, and one cannot be accepted to the exclusion of the other. Both have their faults, and yet both are founded on certain demonstrable facts.

The first attempt at an explanation which gave the slightest ray of hope to the solution of the problems of acquired resistance of the body against the invasion of foreign substances was suggested by that brilliant investigator, Metchnikoff. He studied the behavior of the white blood cells, and attributed the destruction of bacteria in the body to their activities. Others had previously noted that bacteria were at times found in these cells, but Metchnikoff made an exhaustive study of the fact, and upon this founded the Theory of Phagocytosis. The cells which took up and devoured or digested the bacteria were called phagocytes, and of these he recognized two groups—the small phagocytes or white blood cells, and the large phagocytes or cells drived from the endothelial and other tissues of the body. The small phagocytes or "microphages," as Metchnikoff termed them, seem to attempt to defend the body against the acute infectious diseases, while the large phagocytes or "macrophages" pay more attention to the animal parasites, and to the microorganisms which cause chronic infections.

Ehrlich's theory, the Side Chain Theory, on the other hand, is based on the idea that the process of immunity is of a chemical nature; and that the antibody arises from the normal body cells, and has nothing to do with the phagocytes. He believes that the normal body cell consists of a central complex protoplasm, giving it definite and special properties. With the complex protoplasm are associated other combinations, similar to those in the benzol ring in chemistry, which have the function or property of combining with extracellular or outside material, and are called receptors or side chains. In performing the normal and every-day functions, as the assimilation and absorption of food after digestion, certain of these cells in the body have their part to play in the act. The assimilation is due to a chemical union between the receptors of the cell, on the one hand, and the nutrient material on the other, brought to them by the blood and lymph from the digestive apparatus. By means of this chemical union of a receptor and nutrient material, the protoplasm of the cell is fed. As in chemistry, in order for a certain molecule to enter the ring or to be assimilated by the protoplasm of the cell, it must be able to satisfy the affinity of some receptor; so in the every-day functions of the body the nutrient material must find its corresponding receptor, or side chain, before it can enter the cell. Ehrlich's theory, therefore, depends upon the supposition that toxins or poisons, like food or nutrient material, can combine with certain receptors and then enter the cell and destroy it. Ehrlich found that the property of the diphtheria toxin to combine with the antitoxin was constant, while the property of producing disease was variable, and from this was led to believe that the toxin molecule had two parts or groups—the toxic part or toxophore group, and the non-toxic part or haptophore group. He demonstrated, also, that the toxin molecule combined with certain cells, by means of this haptophore group attaching itself to the receptor of the cell. The haptophore group, therefore, is the link which attaches the toxic part of the toxin molecule to the receptor or side chain of the cell, and without it the toxin molecule would have no effect whatever upon the cell. The haptophore group, or combining group, is always constant; while the toxophore group, or disease-producing group, is variable. If the toxin, after attaching itself to the cell, damages it to any great extent, it causes the cell to die. If enough of the cells are thus damaged, the body as a whole is overcome by the poison and fatal results follow. On the other hand, if the cell is lightly affected, as is found in producing artificially active immunity, the cell in losing one receptor proceeds at once to generate and produce others. In this process of regeneration there is an overproduction of these receptors, which are cast off into the system, and find their way to the blood stream, lymph channels and possibly the tissue juices. Although these receptors are cast off from the cells, they are still able to combine with the toxin molecule. The cast-off receptors or side-chains are the antibodies or antitoxins, and by combining with toxin, either in another animal body or in the test tube, will neutralize it and produce a chemically inert substance. The receptor, therefore, becomes an antitoxin as soon as it is cast off, but not until then. These receptors may remain in the individual or animal in which they are formed, and continue to protect the body. This is the active immunity we see following infectious diseases and called naturally acquired immunity, or following forced immunity, as seen in an animal immunized against diphtheria toxin or the tetanus toxin, called the artificially acquired immunity. These receptors may be transferred to another animal body, producing a condition recognized when an individual is injected with antitoxin, either for prophylactic or curative purpose, called passive immunity. In order to satisfy other conditions of immunity, Ehrlich found it necessary to distinguish three orders of receptors. The side-chain theory, in fact, is built up on such an ingenious plan that almost any condition imaginable in immunity may be accounted for by producing other orders of receptors. In the first order we find the simple receptor, which combines with the haptophore group of the toxin molecule. In this order are placed the antitoxins. Agglutinins and precipitins are included in the receptor of the second order, and the cytolysins, including the bacteriolysins, are of the third order.

5. IMMUNITY. We will first divide immunity into Natural, Inherited and Acquired. Natural immunity is the inherent, innate insusceptibility to disease. It is difficult, therefore, according to our present knowledge, to discriminate between natural and inherited immunity. It is a well known and recognized fact that certain species, races and individuals, under apparently the same conditions, are very resistant to some infections, and that others are extremely susceptible to the same infections. Typhoid fever, cholera, diphtheria, scarlet fever, measles, whooping cough, mumps and other diseases occur in man only; animals are naturally immune. Some of the diseases which are found in animals alone are hog cholera (swine), contagious pleuropneumonia (cattle), equine influenza (horses and mules), and blackleg (sheep and heifers). Diseases common to both man and animals are tuberculosis, anthrax, glanders, pyemia, tetanus, plague, actinomycosis, cowpox and many others. There are also exceptions to these. The goat and dog are considered naturally immune to tuberculosis. While ordinary sheep are susceptible to anthrax, Algerian sheep are resistant. Rats are immune to anthrax, while most birds are susceptible. Snake venom is extremely poisonous to both man and animals, with one exception; hogs are immune. The field mouse is very susceptible to the glanders bacterium, while the white mouse is immune. Another very interesting fact which may be considered an example of natural immunity is found in the mosquito. The Culex does not harbor the parasite of malaria, while the Anopheles is its common host. The ability to transmit yellow fever is limited to one particular species of mosquito, the Stegomyia calopus. Individual differences in immunity, or the natural power of resistance under similar existing conditions, occur every day. In an epidemic of typhoid fever, due to a contaminated water supply, some individuals become infected while others do not; and this may occur in the same family. Again, with whooping-cough, scarlet fever, measles or any of the acute contagious diseases of childhood, one of the children in a family may become infected, while the others will remain well. The immunity is oftentimes carried through the lifetime of the individual.

Acquired Immunity. An acquired immunity is that form of immunity gained by a susceptible individual during the life of that individual. It differs from the natural immunity, in being less certain and having a variable duration. We have two varieties of acquired immunity—naturally acquired and artificially acquired.

Naturally Acquired Immunity. Naturally acquired immunity is established as the result of the spontaneous cure of an infectious disease. This is termed by some accidental infection.

Recovery from some of the acute infectious diseases confers a lifelong immunity to the individual, while an attack of others results in a decreased resistance. Smallpox, scarlet fever, typhoid fever, measles, whooping-cough, mumps and other infections produce an immunity which is, as a rule, lasting; although a few cases are recorded of a second and even a third attack, as the length of the immunity does not depend upon the severity of the infection. On the other hand, pneumonia and influenza not only do not produce an immunity, but usually render the individual more liable to subsequent attacks. Some diseases, therefore, produce an increased resistance, while others an increased susceptibility.

Artificially Acquired Immunity. Artificially acquired immunity is produced by intentional inoculation. This may be either for experimental or therapeutic purposes, but always with some definite end in view. This sort of immunity may be active or passive.

Active Immunity. In the active form, the immunized individual gains its power of resistance by the unaided reaction of its own tissues, or in other words, it manufactures its own antibodies. In every case the immunity depends upon specific reactions on the part of the cells and tissues of the individual. The best example of this form of immunity is illustrated in the horse which has been immunized with diphtheria toxin to produce the antitoxin. The animal is injected with a dose of toxin not large enough to prove fatal, but toxic enough to produce a reaction. The horse becomes ill and recovers, the symptoms lasting but a few days. This process is repeated until the animal is able to stand an amount of toxin many hundred times the fatal dose. After the first injection something has changed in the animal, for it will not again react in the same way to the same dose. The cells or tissues of the body have acquired a new property by their own physiological activity, and this is termed active artificially acquired immunity. Such immunity is always gained at the expense, and often at the risk, of the individual acquiring it. There are many different ways of producing this form of immunity. It may be produced either by means of the bacteria themselves or their products. Experimentally we may use the live virulent, the attenuated, or the dead bacteria, but therapeutically the live virulent bacteria are not injected into the body on account of the danger attendant upon such treatment. Wherever possible, for prophylactic purposes, the attenuated organisms are preferable to the dead, because the symptoms are the result of a mild infection, calling forth more of a specific reaction on the part of the tissues and cells of the body, thereby resulting in a more lasting immunity. In preparing these attenuated organisms for the production of active immunity, the more of their natural chacteristics they are allowed to retain, with safety to the patient, the more potent will be the result.

Micro-organisms may be attenuated by mechanical or natural means. The mechanical methods are heat, chemicals, desiccation and dialysis. The organisms are washed or scraped off the solid culture media, are thrown down by centrifugation from the liquid culture media or else are taken as they grow in the liquid culture media and are heated just enough to retard their growth or diminish their virulence. The tissues of the animal body in which the bacteria are growing may be allowed to undergo the same treatment. A typical example of an attenuated product of this last sort is blackleg or symptomatic anthrax vaccine. Subjecting the bacteria in a similar manner to certain chemicals or their fumes may produce the same results. We may also attenuate bacteria, while still growing in the culture media, by subjecting them to heat or chemical influence as in the production of Pasteur Anthrax Vaccine. In growing under these artificial or unnatural conditions, some sort of a change takes place in the micro-organisms. They become less virulent, and when injected, the resulting symptoms are atypical of the disease. The Pasteur vaccine for rabies is attenuated by desiccation. Whether this is in fact an attenuation of the organism or merely a dilution of the virus caused by the death of many of the organisms is a question. We may also attenuate or modify a virus by dialysis. In this manner the immunizing substance, whatever it may be, is allowed to remain intact at the expense of the toxin part of the virus which is apparently dialyzable. The natural method of attenuation is by passing the micro-organisms through certain animals. This is rarely accomplished, but it has been done, as in the case of the passage of the rabies virus through monkeys. The gradual cessation of an epidemic after weeks or perhaps months of the most virulent types of infection is probably often the result of a natural attenuation of the causal organism.

In preparing dead bacteria for immunizing purposes, we strive to kill the micro-organisms, but not destroy their products. Among these products are the endotoxins. We heat the bacteria, or cause them to come in contact with certain chemicals in the form of solutions or gases, just to the point of stopping their growth. Heat has been the generally accepted agent for killing the bacteria used for therapeutic purposes, although suspensions of the bacteria may be made with dilute germicides, as the coal-tar products or other antiseptics, just strong enough to kill them, not to produce an injurious effect upon the therapeutic value of the vaccine or upon the patient receiving the treatment. Here again it must be borne in mind that the more injury to which we subject the organisms, one way or another, the less will be the production of immunity. Heat being recognized as antagonistic to those functions of bacteria which have to do with the production of immunity, it behooves us to use as little heat as possible in the process of devitalizing the organisms. Suspensions of dead bacteria, especially those intended for prophylactic purposes, prepared without the aid of heat, are being recognized more and more as superior to those treated according to the original method. Therapeutically these suspensions of dead bacteria are used in dilute form, and are called bacterial vaccines or bacterins. These vaccines may be used either prophylactically to prevent the invasion of bacteria, or curatively to assist nature in fighting an infection after the invasion of pathogenic bacteria has already been accomplished. It is claimed by some of the best authorities that the older the strain of organisms, the less will be their immunizing properties; therefore, those autogenetic micro-organisms isolated recently from a diseased process are considered preferable to those grown for a considerable length of time away from their natural environments. This is known not to be true for all organisms, especially the typhoid, and it may not hold for any. That the immunizing properties or toxin producing properties of bacteria do not go hand in hand with their disease producing properties is an already known fact. The best toxin producing strain of the diphtheria bacterium with which we are familiar is known to be practically avirulent. If this holds true for the extracellular toxin producers, the same should pertain to the endocellular toxin producers. It is not necessary for an organism to be virulent and young in order to be a toxin producer, and therefore, why should it have to be freshly isolated and virulent to be an immunizer? It is also claimed that certain organisms which are allowed to remain for variable lengths of time in contact with their homologous antiserums will retain their immunizing properties while losing their pathogenic properties. The process of neutralizing the toxic properties of the organism with the antitoxin, termed sensitization, appears to attenuate the organisms without the aid of heat or chemicals.

The bacterial products, or the toxins, which are employed experimentally and practically, for the production of immunity in animals in the preparation of antisera, are the exotoxins and the endotoxins. Of the few exotoxins, only two are used to any great extent, the diphtheria and tetanus. We are unable to use these soluble toxins directly for therapeutic purposes, on account of their extremely harmful specific nature. Immunity is produced with them, as has already been explained in the case of the horse in the preparation of antitoxin serums, but this immunity is forced and at the risk of the individual immunized, so that for therapeutic purposes the treatment would be even more dangerous than the disease itself. A process somewhat analogous to sensitization of bacteria may be mentioned in this connection. It is known that active immunity may be produced by a soluble toxin as the diphtheria toxin, so long as it has been sensitized or even over-neutralized by its own antitoxin before injection. The toxic portion of the toxin molecule is neutralized or rendered inert without apparently modifying the immunizing properties. This principle, which has lately been applied by Behring to the active prophylactic immunization of the human against diphtheria, has been used in this country several years for the production of active immunity in animals, especially the horse, and was suggested several years ago by Smith for use in the human. The idea is not original with Behring. By far the greater number of pathogenic bacteria do not produce soluble toxins in the liquid culture media in which they are grown, but do liberate poisonous products, when the bacterial cells are disintegrated. These poisonous or toxic products are termed the endotoxins, and when injected into animals, immunize them to a certain extent against the invasion of the specific micro-organisms from which the endotoxins were obtained. The serum of the thus immunized animal has become antibacterial. Experiments have shown that it will kill the specific bacteria, by causing them to break up (a condition recognized as lysis) either in the animal or the test tube. It is termed a bactericidal serum with properties called bacteriolytic. Besides containing these substances which kill bacteria, the serum has been endowed with some properties which cause the bacteria to clump together or agglutinate, called agglutinins, and others which render the bacteria more readily ingested by the phagocytes, called the opsonins, and still others which produce a precipitate of the specific or homologous bacterial proteids by means of substances called precipitins.

Active immunity is produced artificially not only with bacterial toxins, but also with animal poisons, as snake venom, spider toxin and eel serum; and plant poisons, such as those extracted from abrin, ricin, cotin and the poisonous mushrooms. From these poisons, which are soluble toxins, antitoxins may be obtained by immunizing animals with them. Of all these animal and plant poisons, snake venom is the only one used for therapeutic purposes. By means of this, an antitoxin is produced which has marked prophylactic properties against snake bites, and is used extensively in countries where the poisonous snakes abound.

Passive Immunity. Passive immunity is that form of immunity which depends upon defensive factors not originating in the animal protected, but artificially supplied to it. The protective material or antibody is furnished ready made at the risk of another animal, and, although the effect is secured at once, the immunity is only temporary. The best illustration is of that immunity produced by the injection of antidiphtheric serum. The diphtheria organisms are grown in bouillon to produce the diphtheria toxin. The horse is injected with this diphtheria toxin and becomes actively immunized to the toxin. The serum which contains the antibody, formed by the tissues of the horse, is injected into the patient suffering with the disease caused by the diphtheria organisms. The antibody is carried from the horse, by means of this serum, to the patient, who becomes immunized to the diphtheria toxin at once. The tissues and cells of the patient, therefore, are absolutely passive in the transaction, for the immunity is actually forced upon them. It is not the result of their physiological activity, hence the term passive immunity. The animal furnishing the defensive material must previously have been actively immunized. Passive immunity may be produced by injecting the following substances which contain defensive materials:

1. Blood serum of animals actively immunized by artificial methods.
2. Blood serum of animals actively immunized by natural methods.

Although the introduction, into susceptible animals, of blood serum of animals actively immunized by natural methods, such as those recovering from an infectious disease, raises their resistance to a certain degree, the immunity is not pronounced, nor is it lasting. The best results are obtained from those animals which are artificially immunized, especially in the production of diphtheria and tetanus antitoxin. The antitoxic serum is formed by the repeated injection of toxin during an extended period of time, while the quantity is pushed to the limit, so that the antitoxic strength or potency (antitoxin units per cc.) of the serum is as high as possible.

Passive immunity may be of two kinds, antitoxic and antibacterial, depending upon whether the individual was immunized with antitoxic or antibacterial serum. The antibacterial serums are not as specific as the antitoxic, and therefore, have not the same relative therapeutic value.

The antitoxic serums are the antidiphtheric and antitetanic. The antibacterial serums are antigonococcic, antimeningitic, antistreptococcic and antituberculic.

(To be continued.)