LOCAL IMMUNITY

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CONTENTS

	Page
Introduction	1
Skin	8
Intestinal apparatus	18
Lungs	25
General Conclusions	29
Bibliography	33

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One of the earliest works on what we understand now by local immunity was done by Loeffler in 1881. He found that the subcutaneous inoculation of the organism of mouse septicemia in the rabbit produces a fatal infection, and a local keratitis on corneal inoculation. According to Loeffler, however, if the rabbit is inoculated on the right ear and then eight days later on the left, no reaction occurs. The cornea, however, is not protected until the third week, which coincides with the appearance of generalized immunity. It would seem here, then, that we have an area of rather localized protection before the general immunity is established.

In 1901, Roemer performed a classic example of local production of antitoxin. He instilled abrin into a rabbit's eye and found that the conjunctiva of the eye developed an antitoxic power against abrin which protected mice against many times the fatal dose, while that of the other eye remained practically inactive.

Hektoen claims that RÖemer's experiments do not prove local production of antibodies. He said that when Roemer made his tests with the conjunctiva, the blood was also antitoxic. "One of the rabbits has been under treatment for six weeks, the other for three, and during this time the conjunctiva in question was repeatedly subjected to the action of increasing quantities of abrin. It consequently is not excluded that the antitoxic action of conjunctival tissue may not have resulted from the passage of antitoxin from the blood and lymph into the conjunctiva. While it is true that the conjunctiva of the untreated eye was devoid of antitoxic power, repeated attacks of inflammation in the eye exposed to abrin would have rendered much more easy the passage of antitoxin into the conjunctiva." The arguments of Hektoen do not seem to me to be very convincing, because a mere inflammation of the conjunctiva would not explain the high antitoxic titer in one eye and none in the other.

Wassermann and Citron,* in 1905, demonstrated that the locality of production of antibodies is largely dependant upon the locality in which the antigen is concentrated. They injected typhoid bacilli into rabbits intraperitoneally, intraneously and intrapleurally, and nine days afterwards determining the comparative bactericidal strength of blood serum and of aleuronate exudates of pleura and peritoneum in each

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*Quoted from Zinsser: Infection and Resistance, p. 102.

of the three animals. Their results showed that the bactericidal titer of the intravenously inoculated animal was highest in the blood serum, while that of the intraperitoneally and intrapleurally inoculated animals was highest in peritoneal and pleural exudates respectively . Another isolated experiment of the same authors, alone successful of a series of similar attempts, would point also to the local production of antibodies. Typhoid bacilli were injected subcutaneously into the ear of a rabbit and the ear immediately ligated at its base and kept so for several hours. After nine days the bactericidal titer of the blood serum was determined and the ear amputated. An immediate and rapid drop of antibody content occurred after the amputation, indicating that the chief source of antibody function has been recovered.

In order to ascertain if antibodies could be produced locally, Hektoen made a series of experiments, injecting goat or rat corpuscles into the anterior chamber of the eye, into the pleura and into subcutaneous tissue of dogs, and he got the following results:

The injection of rat or goat corpuscles into the anterior chamber of the eye of dogs is followed by the appearance of specific antibodies in the blood and usually in the aqueous humor of the injected eye more than in the uninjected,

but in every case it is much less than in the blood. The antibodies do not appear earlier in the aqueous humor than in the blood.

The injection of rat or goat corpuscles in the pleural cavity in dogs is followed by the appearance of specific antibodies in the blood and in pleural exudates evoked by means of aleuronat. The concentration of the blood is probably a little lower than after intravenous injection of the same amount of antigen. The concentration in the pleural exudates is not higher than in the blood, often it is less. There is no difference in the relation between the antibody content of the blood and of the pleural exudate in dogs receiving the antigen in the pleural cavity in question and in dogs receiving the antigen intravenously.

Massage of the tissues of the site of injection of antigen does not seem to increase the antibody content of the blood in dogs. In dogs injected subcutaneously over the foreleg with rat or goat corpuscles, amputation of the injected leg in the early phases of antibody formation does not result in less antibody in the blood than in other dogs in which the same tissues are not removed, the other conditions being equal.

The failure of Hektoen in producing local antibodies is probably due chiefly to the antigen selected for his experiments. The red corpuscles are normally destroyed in the

in the hematopoietic organs and it is there that one would expect to find, mainly, the formation of the corresponding antibodies, and not in the anterior chamber of the eye, the pleural cavity or the subcutaneous tissue.

Smith, Orcutt and Little, by selecting an appropriate antigen, have proved the local production of agglutinins in the cow's udder. The infection of cows by B. abortus is always followed by the presence of agglutinins in the blood and milk. In the majority of cases the agglutinins presented that fraction of the blood agglutinins which has been usually ascribed to a filtration from the blood. The authors having found that many cases could not be ranged in this group, carried out a series of very interesting experiments in order to see of the agglutinins are locally produced in the udder. As a result of those experiments, it appears that after injection of living or dead bacteria into the udder ducts, the increased agglutinin is produced mainly in the udder tissue and that it is not due to an increased permeability of the endothelium or the epithelium of the gland. The quarter of the udder injected acts at first with a heavy influx of polunuclear leucocytes and later with an increase of agglutinins.

Cobbett and Melsome, working with streptococci, have arrived at the following conclusions:

(a) Injection of streptococci or their products in the abdominal cavity confers immunity to a second injection, in the same situation, of more virulent cultures in quantities fatal to control animals.

(b) Cutaneous erysipelas completely protects the parts directly infected against subsequent inoculations of the virus. In other words, it confers an absolute local immunity, while on the rest of the body it confers a general immunity which is less constant, sometimes protecting completely, at other times modifying, the course of the disease, while in some instances it is entirely absent.

(c) Intra-abdominal injections of attenuated cultures of streptococci confer a somewhat more perfect immunity upon the rest of the body.

(d) Both local and general immunity are of short duration and do not last more than a few weeks.

(e) When streptococci are introduced into rabbits' ears, protected by recent erysipelas, an inflammatory reaction quickly appears, and has alreadyssubsided before inflammation has made any considerable progress in the control.

(f) The rapidity of onset, and the intensity of this inflammatory reaction, is most marked in ears locally protected; less marked in those which share in the general immunity produced by intraperitoneal injections and least marked in those which share the general immunity produced by

erysipelas in the opposite ear; that is to say, it is in proportion to the immunity observed in these three classes of cases.

(g) A similar difference in the inflammatory reaction of immunized and normal parts is observed when filtered cultures or dead streptococci are introduced.

(h) That this power of quickly reacting is an important factor of immunity both general and local.

(i) This same power of reacting is acquired during the course of the disease, and is the cause of recovery.

Nobody has contributed so much to the subject of local immunity as Besredka. The early workers, whenever they found an indication of local immunity, attributed it to the local production of antibodies. Besredka, after a series of valuable experiments, arrived at the conclusion that local immunity was acquired primarily without the coucourse of antibodies. Since Besredka's experiments, other investigators have worked along the same line.

In order to facilitate the exposition, I am going to review the studies made by recent investigators in local immunity, as follows:

1st. The Skin.

2nd. Intestinal apparatus.

3rd. Lungs.

1. The Skin. - The skin, when intact, offers to the external influences of infection a strong and efficient barrier. When the continuity is broken even by a small abrasion, an infection can take place. If the microorganism is not virulent enough, or if the skin reacts enough, the infection is localized and cured without any further consequences for the individual. When inverse conditions exist, generalization of the infective organism occurs. This is the case, for instance, with anthrax infection in men. Sometimes the malignant pustule heals without further generalization and in other cases septicemia and death occurs. It is by utilizing the affinity that certain microbes have for the skin that recent investigators have worked out the production of total immunity. We are going to consider the infection of the skin by different organisms and the immunity that takes place.

Anthrax. - Anthrax bacillus has been more often the object of immunological investigation than other bacilli. Vaccination against anthrax was one of Pasteur's discoveries. Since that time it has been the object of numerous investigations and several theories have been offered in explanation of the nature of resistance following vaccination.

In 1888 Behring showed that the rat, which is immune to anthrax has a powerful bactericidal serum and thought that the key to anti-anthrax immunity in general.

When in 1890 Metchnikoff published his classic work the immunity of rats was proved to be a particular case not likely to be generalized. When later workers began to investigate the problem of anti-anthrax serotherapy, the passive immunity was considered. It is known that large animals can be easily vaccinated. Horses can arrive at toleration by intravenous injections of liters of virus. The serum obtained under these conditions protects the guinea pig against the minimal lethal dose.

As can be seen, anthrax immunity was not clearly understood in spite of the great amount of work done in this line. Laboratory animals, so easily vaccinated against different bacteria, could not be vaccinated against anthrax. Recently, Besredka, after having worked on local immunization of intestines and lungs, tried to obtain a local immunization of the skin and selected anthrax for the test. The Pasteur method, which is so effective in large animals, fails almost always with the guinea pig. With patience one can vaccinate by the subcutaneous method, with great difficulty, the guinea pig against the second dose, but when this virus passes the failure is almost certain.

Attempts to vaccinate by the peritoneal method are even less satisfactory. Besredka has shown the surprising fact that one can inject intraperitoneally, without killing the guinea pig, thousands of lethal doses of virulent bacilli,

even without previous injection of attenuated vaccine; that guinea pigs can get the infection only by the skin and is refractive by any other way. According to this author, when one injects the guinea pig with anthrax bacilli in the peritoneum, in the trachea, in the brain, or anywhere, one inevitably passes through the skin and in so doing deposits involuntarily a small amount of virus, sufficient for developing a mortal infection. "If one could imagine the animal without skin and keeping alive, and if one could inject anthrax virus in any part of the body after the removal of the animal from the skin, one would see opposed to the virus a complete indifference." When considerable quantities of the bacteria are injected into the peritoneum these as soon as phagocyted and digested disappear from the body without leaving a trace. The destruction is so rapid and so complete that none of them arrives to the sensitive organ, or in other words, to the skin. The skin being away from the attack of anthrax, the animal ignores the inoculation made; also remains after inoculation as sensitive to anthrax as before; has no immunity.

The skin being the only organ sensitive to anthrax, the interior of the animal being naturally refractive to the disease, Besredka decided to investigate the immunization of the skin, believing that if the skin were vaccinated the whole guinea pig would be immunized. He succeeded in vaccinating the skin by making it accustomed to stronger and stronger virus,

given either by intracutaneous inoculation or by simple rubbing of the skin after the animal was shaven. In that way not only the skin but the whole guinea pig became vaccinated against anthrax, and hundreds or thousands of lethal doses of virus could furthermore be inoculated without any inconvenience.

The Pasteur method of vaccination of large animals is not always successful in the immunization against inoculation of blood containing anthrax bacilli. This is explained by the fact that the capsule which envelops the bacillus in the blood paralyzes the phagocytes, and lessens in that way the immunity. In order to see if a guinea pig immunized by his method could resist the inoculation of blood containing anthrax bacilli, Besredka inoculated several guinea pigs with such blood in varying amounts. He found that the cuti-vaccination of guinea pigs with anthrax bacilli from cultures protected the animals against the bacilli contained in the blood of animals dead from anthrax, at least to the amount of two hundred lethal doses.

Besredka's work of anthrax immunization of guinea pigs has been completely confirmed by the experiments of Balteano. He injected guinea pigs in the peritoneum, pleural cavity, and under the skin, without producing infection when the skin was not contaminated, and describes various ingenious

methods by which he evades the skin during the inoculation. He has also succeeded in immunizing guinea pigs and rabbits by Besredka's method.

In order to see if the immunized guinea pig contained protective antibodies, Besredka made the following experiment: From a strongly immunized guinea pig he took serum and injected two new guinea pigs with a dose of 1 c.c. each. These two animals were inoculated the following day with a lethal dose (M.L.D.?) of virus, as well as some controls. The guinea pigs previously injected with serum as well as the controls, died at the same time. Besredka concludes from this experiment that immunization against anthrax is not due to antibodies.

This experiment does not seem to me entirely probatory. It might be that 1 c.c. of serum does not have enough antibodies to protect a new guinea pig but that a larger amount would. On the other hand, he does not state if the lethal dose used was the M.L.D. and that would, of course, be of great importance.

What is the mechanism of immunity against anthrax? Not enough research work has been done along this line to answer the question satisfactorily. In spite of Besredka's explanations, it is not clear how the whole skin can become immunized by inoculating only one point by virus. The different portions of the skin have no other means of communication

but by the circulatory system, and therefore the factors producing immunity must be carried by the circulation. Are these factors, substances produced by disintegration of the bacilli and carried by the circulation, going to act upon the whole skin? In that case the disintegration of the bacilli injected by any other method would have the same effect and we know that is not the fact.

The process of immunity is probably not exactly the same in large animals as in laboratory animals. We know that large animals can acquire infection by the intestinal mucosa as well as by the skin and that they can be immunized by other ways than intradermally. We know that the contrary happens with small laboratory animals.

Vaccina. - We quote from Bordet (T. de l'Immunite, p. 680) the following paragraph:

"In 1892, Béclère, Chambon and Menard, noted that the serum of the organisms treated by vaccine virus or of the ones cured of smallpox makes the vaccine inactive. The remarkable fact which proves the role of antibodies is that the lymph of the vaccinal pustule loses its virulence just at the moment when the antivirulici/dal activity appears in the blood, that is, at about the end of a week. The production of cutaneous lesions are not at all indispensable to the production of immunity. The subcutaneous or intravenous inoculation of

lymph gives the refractive state. It protects the skin against the effect of inoculation (Chauveau). It is naturally capable of producing antibodies. In preventative injection the immune serum, when it is very active, can prevent the formation of pustules with vaccine. In this respect it is by intravenous injection that the serum shows more efficacy (Henseval et Covent)."

The viruscidal antibodies which appear in the course of vaccination have been considered as the expression of antibodies. Besredka, on the contrary, has obtained results entirely different from the principles above stated and found a complete parallelism to anthrax in the mechanism of this infection. He states that if one is careful not to contaminate the skin, one can inject virus into the peritoneum of the guinea pig without any effect. Although the viruscidal antibodies make their appearance, a new attack of virus carried over the shaved skin finds the animal receptive to the same titer as a new rabbit. The contrary occurs when applied over the shaved and depilitated skin. The vaccine gives rise after a period of incubation of four to five days to cutaneous eruption that one knows of. Immediately upon its appearance, even before the papules have had time to dry, one finds that the skin has become vaccinated. A new attack similar to the former finds the animal completely indifferent.

The viruscidal antibodies coming from a rabbit properly vaccinated do not act except when they come into direct contact with virus. These antibodies do not act at all when the virus and the antibodies are separately injected. Besredka further states that there is no parallelism between the titer of the serum in a viruscidal substance and the degree of immunity. The viruscidal substance disappears from the blood at the end of two or three months but the immunity can persist for a very much longer time. Finally, after the cutaneous inoculation of virus the epidermis acquires a late immunity sometimes when the antibodies exist only in traces or not at all.

If all these statements can be confirmed, there is certainly a parallelism in the mechanism of immunity in anthrax and smallpox vaccination. How close this analogy is, it is very difficult to ascertain at the present time. Local immunity is probably an important factor in smallpox vaccination, but in the presence of viruscidal antibodies, one cannot help thinking that they also play an important part, at least at the beginning of the process of immunization.

Streptococcus infections. - Mention is made in the literature of many examples suggesting local immunity in cutaneous streptococcus infection. In erysipelas, for instance, the process extends along the edges, while the original central area of infection is returning to the normal state, and

and it rarely occurs in adults that the erysipelatous process extends back into the originally infected area. (Zinsser.)

Levaditi, in studying the evolution of war wounds infected with streptococcus, discovered an interesting fact concerning local immunity. In his experiments he shows, that when one tries to reinfect a wound that has become astreptococcic, with material from other wounds still contaminated in the same individual, there is very little chance of infection. Either the microbes die out or remain there for a day or two. The same occurs if the experiment is carried on with the culture of the microbe (homologous streptococcus). On the contrary, a reinfection can take place easier if one uses a virulent streptococcus taken from some other individual (heterologous streptococcus). Here we find a local immunity in certain wounds, more pronounced for a particular strain. Levaditi suggests that this might have a practical value, such as the active vaccination of wounds by early application to the wound of dead or autolysed microbes.

Gay has carried out experiments in rabbits proving to a measureable degree the local immunity following streptococcus infection. He used a strain originally isolated from a case of human empyema and made more virulent by means of frequent passage through the pleural cavity of rabbits and maintained at a constant virulence by conservation in pleural fluid.

With this culture he was able to produce erysipelas regularly with a dose of 0.1 c.c. of a twenty-four-hour broth culture. The animal recovers perfectly, although twice this dose leads to a fatal septicemia. "Recovery from erysipelas protects an animal completely against re-inoculation intradermally elsewhere on the body. It does not, however, protect the animal against intravenous inoculation with the same dose and it should further be mentioned that the minimal lethal dose is practically the same intravenously as is the symtomatic dose intradermally. Intravenous inoculation of sublethal doses protects the animal against intravenous inoculation. but does not against intradermal inoculation."

Hay Fever and Bronchial Asthma. - A very interesting set of experiments has been carried on by Mackenzie and Baldwin in regard to local desensitization on hay fever and bronchial asthma. They show by their experiments that in individuals manifesting cutaneous hypersensitiveness, the reaction of the skin may be abolished locally by repeatedly applying to the same skin area the substance to which the individual is hypersensitive. The reactivity of the skin at the exhausted site may not return for three days or longer, and this exhaustion appears to be specific. The extent of the area of the exhaustion is strictly limited to the site of the reaction. As can be seen, this phenomenon is a local process and certainly not a general one. This suggests that the local

exhaustion of reactivity depends upon a union of the test substance with something within the cells and that as a result of this union the constituent of the cells participating in the reaction is used up or becomes unavoidable; that subsequently this intracellular reacting substance is released from the union or that it is formed, enabling the cells to react again. The same authors state that they have begun, also, to use this principle therapeutically in hay fever and allergic rhinitis with such substances as Florentine orris (a frequent constituent of face powder) and horse dander. From what they have observed in the treatment of these patients, it is clear that the local application of pollen, horse dander or orris extract brings about an alteration of the reactivity of the nasal mucosa toward these substances with the result that local tolerance is greatly increased. In some of the patients, after four to six weeks of daily application of the substance to which the patient is hypersensitive, the nasal mucosa has tolerated without reaction, more than a thousand times the amount which at the outset caused marked symptoms.

INTESTINAL APPARATUS

Under natural conditions of infection, the dysenteric, choleraic and typho-paratyphoid bacilli have a single port of entrance - the mouth. Animals are protected better than man against oral contamination by a series of disposals

which are echeloned in the form of mechanical barriers or in the form of secretions throughout the length of the digestive tract. There is no such barrier when the bacilli penetrate through an occasional port of infection such as the peritoneal, intravenous or subcutaneous port, and they find their way to the elective organ, the intestine.

In trying to prove the local immunity of the intestine, Besredka has worked with dysentery, cholera and typhoid-paratyphoid infection, experimenting with rabbits.

Dysentery. - Besredka points out that if one injects a proper dose of dysenteric bacillus into the marginal vein of a rabbit's ear, this animal will die in twenty-four to forty-eight hours. In making the autopsy immediately after death one will find the Shiga bacilli only in the intestinal apparatus,which from the gall bladder to the caecum will be coated with them.

Instead of spreading through all the viscera in a uniform way, the dysentery bacilli carried by the blood take refuge in a single organ, and an organ that is less directly in their course. Evidence of the affinity of the dysentery bacillus for the intestine is particularly observed when one selects as the port of entrance the subcutaneous tissue. Despite the length of travel separating the skin from the intestines, the Shiga bacilli are always found in the intestinal

contents. Therefore, since the intentinal apparatus is the only sensitive organ, Besredka endeavored to render it unsensitive; in other words, to vaccinate it. The Shiga Bacillus, which autolyses itself very easily, liberates an endotoxin which acts strongly on the tissues in general. It is by virtue of the desquamating power of their endotoxin that this bacillus can easily reach the receptive cells of the intestine, when given per os. Besredka easily immunized mice and rabbits by making them swallow killed dysentery bacillus. In a short time they acquire an immunity toward live dysentery bacilli and they withstand, after this, by oral, intravenous or peritoneal method of injection, a dose which kills a control within twenty-four hours. According to Besredka, the immunity of the intestine is sufficient to make the whole organism refractive.

The administration by mouth of killed bacilli produces agglutinins only after the first ingestion. After the first administration agglutinins are not formed in the blood. The same is true for the preventive substances. One cannot fine them after repeated administration by mouth of killed bacilli.

Besredka concludes: "The immunity is established without contribution of antibodies; they cannot be found in the blood after immunization by the oral method. It is a local intestinal immunity."

We do not know if the mechanism of immunization is the same in small laboratory animals as in man. But we do know that a man who becomes infected with dysentery bacilli per os under natural conditions, shows protective substances in the blood after recovering from the disease. The success of the andysentery serotherapy shows that at least local and general immunity are established side by side, corresponding to the localization of bacillus in the intestine and the generalization of toxin in the organism of dysenteric patients.

Nicolle and Conseil have succeeded in vaccinating men against dysentery. Having observed that in tunes the natives are ordinarily immune by repeated ingestion of polluted water (process similar to Besredka's oral immunization), they selected for this experiment four white men. Two of these men were prepared by oral administration of massive doses of liquid vaccine and tested fifteen or eighteen days after the last ingestion with virulent cultures, as well as the two men used as controls. The two prepared men did not show any symptoms and the two controls developed dysentery with Shiga baccillus in the feces.

Nicolle and Conseil made a similar experiment also with M. melitensis, with successful results.

Paratyphoid B Bacillus and Cholera Vibrio. - Rabbits can tolerate enormous quantities of cultures of typhoid

paratyphoid or cholera vibrio per os, without being infected. Besredka's experiments show that it is the superficial layer which protects the intestine from being infected, and if this barrier can be removed the rabbit can be infected with paratyphoid B bacillus. In order to remove this barrier he gives beef bile by mouth, which produces a desquamation of the mucosa, and afterwards makes the rabbit swallow the microorganism. After three or four days the rabbit shows diarrhea, loss of weight, subnormal temperature, and in using recently isolated bacilli the animal dies in a short time. Cultures of the intestinal content give colonies of paratyphoid bacillus, very often in pure culture.

The affinity of the paratyphoid B bacillus for the intestinal wall is manifested with the same clearness as with the Shiga bacillus, each time the virus is injected into the general circulation or even when the injection is made in the subcutaneous tissue itself. The bacillus can be found in the intestine and can be found only there.

Besredka got similar results in working with cholera vibrio.

The intestines of man are particularly sensitive to ingestion of even minute doses of bacillus and they acquire an immunity after an attack of typhoid or cholera lasting,

generally, throughout life. The result would be the same in rabbits as in man except that the superficial layer of their intestinal mucosa must be removed. If this is done by means of bile and followed by ingestion of typhoid bacillus alive or killed, one creates immunity.

It is the same for cholera vibrio: If the rabbit is ingested with cholera vibrio after being previously sensitized by bile, and later on subjected to an intravenous inoculation of a lethal dose of cholera, it survives indefinitely.

According to Besredka, this immunity is not due to antibodies. "One finds none in the course of the elaboration of the antianthrax immunity. One finds them, it is true, in the beginning of the anti-typhoid and anti-cholera immunization. But these antibodies, which disappear, on the other hand, as the immunization per os is advanced, do not play an active role in immunity; they only witness the intestinal permeability, observed at the beginning from the action of bile." The fact that man, after recovery from typhoid fever, often shows a negative Widal test although remaining immune, seems to support Besredka's interpretation.

Zingher and Soletsky made a series of experiments with rabbits in an attempt to confirm Besredka's experiments but were not successful. From their experiments they drew the

following conclusions:

1. No immunity was obtained in rabbits prepared with ox-bile and given living or dead paratyphoid B bacillus per os.

2. No agglutinin production was noted in rabbits receiving living or dead bacilli per os either with or without bile.

3. The intravenous fatal dose of paratyphoid B for rabbits prepared with bile is only about one-tenth of the amount required to produce a fatal infection in rabbits which were not so prepared.

4. The killed vaccine of paratyphoid B is more toxic than the suspension of living bacteria.

Valliant has recently confirmed Besredka's work in man, working with vaccine in Pas-de-Calais, having the value of a laboratory experiment. This work was done in the course of a severe epidemic: fifty cases of typhoid fever were registered among 600-650 inhabitants unvaccinated.

Among 173 people vaccinated by the subcutaneous method with T.A.B. vaccine, four cases of typhoid fever were noted, occurring ten to fifteen days after vaccination. The remainder of the population were submitted to oral vaccination with biliated vaccine. Among 1,213 people so vaccinated, only two light cases were registered, which occurred during

the ten days after the ingestion of vaccine.

In all these intestinal infections the immunity is produced, according to Besredka, by contact of the micro-organisms with the intestinal cells. No matter in which way the bacteria is injected, or if dead or alive, they always reach the intestines, and it is only then that immunity is produced. When we give a subcutaneous injection of vaccine, it becomes effective only after having reached, at the end of a long journey which has been imposed, the receptive cells of the intestinal wall. The superiority of the intravenous method, from the point of view of vaccination, lies in the fact that the vaccine which is carried in this way is able to arrive with greater facility, at its destination, in other words the intestines, without suffering sensible loss en route. "For this reason", says Besredka, "the less round-about method conducing directly to this end, consequently the most reasonable, is the oral method; it is also the one which secures the maximum security."

LUNGS

The epithelium of the pulmonary apparatus presents a strong barrier to the penetration of microbes into the organism. One can get an idea of the strength of this barrier by comparing the tolerance of the animal for a microbe inoculated intratracheally with the tolerance when inoculated intravenously.

In order to see if this resistance of the lungs could be further increased, Besredka carried out experiments on guinea pigs by injecting them with Bacillus Diphtheria. These experiments have shown that the Loeffler bacillus is much more easily tolerated by the pulmonary route than intravenously, and that this tolerance can be artificially increased.

Besredka injected a series of guinea pigs in the trachea with killed diphtheria bacilli three consecutive times. Control guinea pigs were also injected in the same way, with killed diphtheria bacilli subcutaneously. In testing these pigs it was found that the ones receiving the injection intratracheally could support a surely lethal dose of live diphtheria bacilli by the trachea. On the contrary, the ones injected subcutaneously were not in condition to survive the test.

Such immunized guinea pigs showed an absence of antibodies. For this reason Besredka drew the conclusion that the survival of the guinea pigs was due to a new property: To a local immunity acquired by the lungs.

Tubercle Bacillus. - Besredka has not been able to determine from his experiments in this line if the local immunity of the lungs can be increased by intratracheal injections of tubercle bacilli, but he has made a very interesting observation: That after injections of tubercle bacilli

by the intratracheal method, the antibodies are more abundant and more persistent than the ones produced by any other method.

Pneumococcus. - Very recently, Cecil and Steffin have given a clear example of local immunity of the lungs by injecting monkeys with pneumococcus. They first tested the effect of three large doses of pneumococcus vaccine injected intratracheally, using the same dose as for subcutaneous injection, namely 120,000,000,000 pneumococci. The injections were given at intervals of five to seven days and the immunity of the monkeys was tested two or three weeks after the third administration of vaccine, by inoculating the immunized monkey intratracheally with small doses (0.001 to 0.0001 c.c.) of living virulent pneumococcus culture. The three vaccinated monkeys remained perfectly well. The control monkeys became ill shortly after inoculation with the virulent pneumococci and ran a typical course of pneumonia. Pneumococcus Type I was used in this test. No protective substances against pneumococcus Type I could be demonstrated in any of the serums, even when doses of culture as minute as 0.0,000,001 c.c. were used.

After this experiment, another was made in order to determine whether three small doses of pneumococcus vaccine injected intratracheally would confer an adequate immunity. The total dosage of vaccine injected was equivalent to approxi-

mately one-tenth of the total dosage employed in the first experiment.

One of the monkeys whose feet was infected developed pneumonia after inoculation with living pneumococci. The other two remained healthy in spite of the inoculation. The control developed pneumonia. The failure to immunize one of the monkeys has been explained by the authors by the existing infected feet, lowering its resistance. A similar result has been observed in man. The successful immunization of monkeys by three small intratracheal doses of vaccine indicates that immunity is more readily induced by the intratracheal route than by the subcutaneous route."The immunity induced by the intratracheal injection of pneumococci vaccine is probably, to a great extent, a cellular immunity. Protection tests were carried out with the serum of all the monkeys vaccinated and in only one case could any protective substance against pneumococcus be demonstrated!

GENERAL CONCLUSIONS

Certain micororganisms have an elective affinity for certain organs. No matter in which way they are injected, they always affect, primarily, a certain part of the body. Most of these microorganisms affect the body without the production of exotoxin, or at least this does not play the main part in the infection. If one injects (Calmette and Guerin) the vaccinal virus into the ear vein of a rabbit, and shaves a small area on the skin of the abdomen, the virus is localized over such area, producing typical pustules. Rabies virus, no matter where it is injected, always goes into the central nervous system. If the animal is dead from rabies, the brain, medula oblongata and spinal cord contains the virus in great quantity; the blood, the muscles and the viscera do not contain it. The unknown rheumatism virus infects primarily the articulations and endocardium. We have already considered the organ affinity of anthrax, cholera, typhoid-paratyphoid, etc. bacilli.

When we consider the immunity following an infection produced by any of the above mentioned microorganisms, we do not find antibodies; or if we do find them, they are of very little value as protective substances. The humoral or the phagocytary theory of the mechanism of immunity cannot be applied in such cases. In order to account for the immunity

we have to admit the existence of local immunity. If a given organism is not developed in the whole organism, but only in a particular organ, it is logical to conclude that this is the one which is going to fight it, and if this battle is won, the cells of the sensitive organ will become more resistant to the infection; in other words, they will be immunized. The intimal process of this kind of immunization is not worked out yet but the experiments previously reviewed prove its existence.

Immunity and antibodies have been considered inseparable for a long time in the minds of immunologists. Reviewing the experiments previously exposed, we see that in speaking of immunization, the production of antibodies is not necessarily implied. This does not mean that antibodies are not useful. They do not appear when the infection is strictly localized, but as soon as this is spread, antibodies appear as the means of general defence against the pathogenic organisms.

Antibodies are the main factor in the process of immunization against microorganisms, actuating mainly by their exotoxins. Diphtheria and tetanus bacilli act upon the organism almost exclusively by their toxins; and the organism opposes the infection by producing an antitoxin. The role played by these antibodies is so important that we can measure

the degree of immunity by the amount of antibodies present in the blood. On the other hand, anthrax infection does not give rise to the production of antibodies, although a strong immunity follows. Between these two extremes we find a whole intermediate scale. In the majority of infections, local and general immunity are produced side by side, according to many factors: More or less affinity of the organism for a particular organ, portal of entry, the way by which the microbe acts upon the organism, the relative importance of toxins in the infection, the virulence of the microbe, previous conditions of the organs, etc.

The practical importance of local immunity will probably be great in the future. We have already reviewed the successful attempts at vaccination in man by oral immunization. Besredka considers that Wright's method of vaccination is only a cutaneous vaccination which ends in case of cure in a cutaneous immunity. The main success of this method has been in cutaneous affections of the skin, produced by staphylococcus and in some cases by streptococcus, and Wright and his followers give to antibodies the credit for immunization by this method. But we see that in such cases antibodies are difficult to produce and are of doubtful protective properties. If the process is merely a local immunity, as Besredka believes, the best way to inoculate the vaccine would be by the intracutaneous method.

The great interest that the recent work in local immunity has aroused among immunologists will contribute, undoubtedly, to the clearing up of obscure points in the mechanism of immunity, and to more rational methods of disease prevention.

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