

# On the Present State of the Question of Immunity in Infectious Diseases

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I am here before you by virtue of paragraph 9 of the Statutes of the Nobel Foundation, which states that "it shall be incumbent on a prize-winner, whenever this is possible, to give a public lecture on a subject connected with the work for which the prize has been awarded, such a lecture to be given within six months of Commemoration Day, in Stockholm".

I have had the great honor of receiving, together with my excellent friend, Professor Ehrlich, the Nobel Prize for Medicine "for work on immunity", so that it is on this subject that I shall speak. Since the study of immunity is a chapter in medical theory, and theory is often hard to expound to an audience unequipped with the special notions implied, you see the difficulty that lies before me. Fortunately, the theoretical problem on which I shall enlarge concerns the resistance of the body to the disease. Whatever concerns health is of real public interest. I take advantage of this to make my address less arduous for you. I shall moreover use the opportunity to show you the practical value of pure research.

There is no need to be a doctor or a scientist to wonder why the human body is capable of resisting so many harmful agents in the course of everyday life. It is often seen that in households where all members are exposed to the same danger, or again in schools or troops where everyone lives the same life, disease does not strike everyone indifferently. For some individuals who go down at the attack, there are others who have immunity to a greater or lesser extent.

There used to be only a vague answer to the problem of the body's resistance, remarkable as it is. Since the memorable discoveries of Pasteur and his co-workers who found that immunity could be conferred by means of vaccination with microbes, the question has all at once become vastly clarified. The problem has become open to study by experiment. For Pasteur, who was a chemist, the fact that the undamaged organism does not allow certain morbid agents to spread within it, could be explained simply in terms of the chemistry of the environment. In the same way that plants will not grow on soil that lacks some substance indispensable to their growth, so microbes, these microscopic plants which cause infectious disease, are unable to grow in an organism which does not give them all the substances they need.

This theory is completely logical but contradicted a number of factors to be found in the protected organism. Pasteur and his fellow workers realized this themselves when they found that infectious microbes develop very well in the blood of animals that enjoy complete immunity.

The animal organism is very complex and for this reason it is often hard to explain in simple concepts the phenomena to be observed. To achieve the purpose, a different approach has had to be called for. It has been necessary to look from the point of view of biology, and attempt to simplify research conditions without going beyond the scope of the living organism. This is the idea that has been behind our research. Disease is not the prerogative of man and the domestic animals, so it was quite natural to see if the lower animals, with very simple organizations, showed pathological phenomena, and if so, infection, cure and immunity could be observed among them.

To solve medical problems, comparative pathology had to be called in.

While studying the origin of the digestive organs in the animal world, we were struck by the fact that certain of the organism's elements which have no part to play in the digestion of food are nevertheless capable of storing foreign bodies. For us, the reason was that these elements had once been part of the digestive system. This question of pure zoology has no further place here, so we will only stress the general outcome of our research in this field, which was that the elements of the organism of man and the animals, gifted with autonomic movements and capable of enveloping foreign bodies are no more than remains from the digestive system of primitive beings.

Certain of the lower animals, transparent enough to be observed alive, clearly show in their midst a host of small cells with moving extensions. In these animals the smallest lesion brings an accumulation of these elements at the point of damage. In small transparent larvae, it can easily be shown that the moving cells, reunited at the damage point do often close over foreign bodies.

Such observations on the one hand confirmed our assumption on the origin of these migrant elements, while on the other they suggested that accumulation round lesions is a sort of natural defense on the part of the organism. Some method had to be found by which this hypothesis could be verified. I was at this time - more than twenty five years ago - in Messina, so I turned to the floating larvae of starfish, which had been found for the first time on Scandinavian shores and called *Bipinnaria*. Large enough for several operations, they are transparent and can be observed alive under the microscope.

Sharp splinters were introduced into the bodies of these *Bipinnaria* and the next day I could see a mass of moving cells surrounding the foreign bodies to form a thick cushion layer. The analogy between this phenomenon and what happens when a man has a splinter that causes inflammation and suppuration is extraordinary. The only thing is that in the larva of the starfish, the accumulation of mobile cells round the foreign body is done without any help from the blood vessels or the nervous system, for the simple reason that these animals do not have either the one or the other. It is thus thanks to a sort of spontaneous action that the cells group round the splinter.

The experiment I have just outlined shows the first stage of inflammation in the animal world. Now inflammation as understood in man and the higher animals is a phenomenon that almost always results from the intervention of some pathogenic microbe. So it is held that the afflux of mobile cells towards points of lesion shows the organism's reaction against foreign bodies in general and against infectious microbes in particular. On this hypothesis, disease would be a fight between the morbid agent, the microbe from outside, and the mobile cells of the organism itself. Cure would come from the victory of the cells and immunity would be the sign of their acting sufficiently to prevent the microbial onslaught.

This deduction, based on the fundamental experiment with the splinter in *Bipinnaria*, had to be checked by observations and specific experimentation. Luckily for us, it is not only man and the higher animals that are subject to infectious diseases. These diseases existed on the earth long before the appearance of the human race and few are the creatures which escape them.

Therefore, to demonstrate the value of the hypothesis I have mentioned, some higher animal was needed, small and transparent enough to be observed living under the microscope and yet subject to microbial disease.

Several starts were made. It became possible to study the progress of infection in fresh-water animals, commonly known as "water-fleas". These small crustaceans abound in all kinds of stagnant water and are subject to various diseases. One is caused by a tiny microbe characterized by the production of spores in the shape of needles. Swallowed by the water-fleas or *Daphniae*, which is the scientific term, these spores readily damage the intestinal wall and penetrate to the body cavity. Once they have insinuated themselves into the organism's inmost part, the spores cause an accumulation of the mobile cells round them, which correspond to the white corpuscles in human blood. A battle takes place between the two elements. Sometimes the spores succeed in breeding. Microbes are generated that secrete a substance capable of dissolving the mobile cells. Such cases are rare on the whole. Far more often it happens that the mobile cells kill and digest the infectious spores and thus ensure immunity for the organism.

This description is from a living animal and can be observed at each stage under the microscope with such precision as could hardly be bettered.

The results obtained from the larvae of starfish and from disease in water-fleas form the bedrock of the theory that I am here to expound. This theory came under heavy fire from the greatest names in science and there was some doubt that such an attack was to be withstood. The memory of the *Bipinnaria* and the splinter surrounded by mobile cells and the *Daphniae* with their blood corpuscles devouring the dangerous spores of the infectious microbe, these gave me hope to fight on. Controlled observations on living organism can not be wrong.

Having established the base of the theory of immunity, it had to be applied to the higher organisms and even to man himself. Conditions were incomparably more complex than in the little transparent creatures, and difficulties arose on all sides. Given the impossibility of submitting a vertebrate, even the smallest such as a new-born mouse, to direct examination by microscope, a more complicated way had to be taken, by combining the results of research on the blood and organs extracted from the organism, and thinking out the interconnection. In such circumstances, the door is wide open to mistakes of all sorts.

The study of various infectious diseases in man and the higher animals showed first that the facts observed corresponded very satisfactorily with the theory based on research on the lower, transparent animals. Whenever the organism enjoys immunity, the introduction of infectious microbes is followed by the accumulation of mobile cells, of white corpuscles of the blood in particular which absorb the microbes and destroy them. The white corpuscles and the other cells capable of doing this have been designated "phagocytes", i.e. devouring cells, and the whole function that ensures immunity has been given the name of "phagocytosis".

It has been established as a general rule that in all cases of immunity, natural or acquired, either by preventive vaccination or following an attack of infectious illness, phagocytosis takes place to a marked degree, whereas in fatal or very dangerous diseases, this phenomenon does not exist at all or is attenuated. This rule was demonstrated for the first time on animals immunized against anthrax. When the anthrax bacillus is injected under the skin of sensitive animals, such as the rabbit or the guinea-pig, the microbe is found free in abundant fluid from which the white corpuscles are almost wholly absent. When however the same inoculation is carried out on a rabbit or a guinea-pig that has been previously vaccinated against anthrax, a very different picture results. The bacilli are within a short space of time seized by the white corpuscles which accumulate in quantity at the inoculation point. Once inside the phagocytes, the bacilli die within a comparatively short time. It happens on occasion that only a few hours after the absorption of the bacilli by the white corpuscles, the bacilli are dead.

In time the same rule has been extended to cover a whole host of other infectious diseases. Every time the organism enjoys immunity, the infectious agent falls prey to the phagocytes that gather round the microbes. This general law has even been verified by studying pathogenic microbes, discovered since the law was formulated. With plague, in all cases where the organism is refractory, the plague bacillus is devoured and destroyed by the phagocytes, while in fatal cases of plague the majority of the microbes remain free in the organism's fluids and multiply without hindrance.

To date we have found no exceptions worthy of note to this rule. It is true Weil of Prague has maintained in several publications that in cases of immunity regarding the cholera microbe in hens, the refractory organism meets the microbial invasion by other means than phagocytes. He bases his case on the impossibility of finding this microbe inside the white corpuscles in animals that are resistant to illness. This exception is not a true one. It is explained by the minute dimensions of the cholera microbe in hens, owing to which it easily eludes the eye of the beholder. Soulima examined this question very thoroughly in my laboratory and he found it to be true that, in accordance with the general law, in animals refractory to the cholera

bacillus of hens, it is again the white corpuscles that take hold of the microbe and cause it to disappear within themselves.

Opposers of the phagocyte theory have long taken the view that the white corpuscles and phagocytes in general are only capable of absorbing microbes that have first been killed by the humors of the organism, namely blood plasma and exudative fluids. It would today be hard to find anyone who still maintains this view. Many accurate experiments have shown that the phagocytes surround the infectious microbes while these are quite alive and in a condition where they are capable of bringing fatal infection to the organism that does not enjoy immunity.

The results which I have thus summarized have been achieved after many a long year of research and discussions. Many scientists still kept to the old idea, that the white corpuscles represent an element hostile to health. In serious illness, collections of pus used to be met with. This was thought to consist of white corpuscles only, as the microbes were too small to be detected by the imperfect tools of microscope research. It was supposed that the pus corpuscles themselves might be the source of disease found in the morbid alteration of our cells. When later microbes came to light inside the white corpuscles, it was admitted that the corpuscles, as ill-omened elements in our body, only serve to feed and spread the body's worst enemies, namely the agents of infection. The destruction of these in cases of immunity was rather attributed to the direct influence of the organisms's fluids.

The theory of the bactericidal action of the humors was brought in against the phagocyte theory. To the organism enjoying immunity, natural or acquired, was attributed the power of destroying the infectious microbes without any real assistance from the live cells. This affirmation was based on well-known instances, in which blood and blood serum taken from the organism proved able to kill a considerable quantity of infectious microbes. This theory of the humoral immunity met multiple and major contradictions from the outset, yet it was not without ardent support. The discovery of Pfeiffer was of great assistance to the theory, for he demonstrated the destruction of cholera vibrios in the humor of the abdominal cavity in animals immunized against this microbe. This case has become classic. The vibrios do not die within the phagocytes but in the fluid of the peritoneal secretion. Every attempt was made to show that this was not a case of an exception to the rule, but the demonstration of a general law of immunity. But, after years of hard research, it has been conclusively shown that the vast majority of infectious microbes can not be destroyed by the liquids of the organism and that the instance of the vibrios is to be explained by their extreme fragility. It was also maintained that the destruction of the vibrios by the humors took place by means of the bactericidal substances released by the white corpuscles present in the abdominal cavity. In cases where the very microbes had been introduced to regions of the organism where there were no white corpuscles already in existence, then the destruction of the vibrios was done within the phagocytes which came on to the field of battle. Even in the abdominal cavity, the extracellular destruction of the vibrios was easily to be avoided if the white corpuscles were prevented from suffering and thus from spreading their bactericidal substances. This experimental observation was denied by many observers over a period of years. It was however conclusively confirmed some years back by Bail of Prague. It has thus

been clearly shown that as long as the white corpuscles are intact, the destruction of vibrios in the organism that has immunity takes place within the phagocytes.

Thorough analysis of the phenomena of immunization, an analysis based on extremely numerous experiments, has shown that phagocytosis is in truth a defense action on the part of the organism against the agents of disease. Several of the former supporters of the exclusively humoral theories of immunity later came round to the cellular theory, with more or less important reserve, however. So various intermediate theories were adduced, according to which the organism, threatened by microbial onrush, brought all its resources into play: phagocytes and humors. For some, the destruction of certain infectious agents in the cases of immunity was by the organism fluids, especially the blood plasma, while other microbes had greater resistance and were only killed within the phagocytes. This eclectic theory was developed in the main by your compatriot, A. Pettersson.

For this defense action, the organism would make use of two classes of bactericidal substances, one of which would be circulating in the blood fluid and flow thence to the exudations formed round the microbes, while the other group would only be found within the phagocytes. The first category would react first and foremost on the cholera vibrio, typhoid bacilli and their congeners, while the other would destroy anthrax bacilli, suppuration microbes and others as well.

Just as there were two diverse bactericidal functions of the organism, so the nature of the substances that destroy the microbes would be diverse. The bactericidal substances of the humors would be of complex nature, consisting of a substance that would prepare the microbes, without damaging them, for the action of the substance that would kill them. Various names were put forward to designate these two substances. Ehrlich gave the name of amboceptor to the preparatory substance and the name of complement to that which destroys the microbes. Not to complicate further matters that are very complicated already, we shall use the terms proposed by our eminent colleague, without sharing his view of the actual part played by the two substances.

Formerly, I mean to say ten years and more ago, certain scientists thought that the bactericidal substance proper, although circulating in the blood fluid, was nevertheless a secretion of the white corpuscles. Of late more and more voices state the contrary to be the case. It is readily admitted that the complement has nothing to do with the corpuscles and has a completely different origin. This view is based on much research carried out with extracts prepared from the white corpuscles taken out of the organism. To this end, exudations that are very rich in these corpuscles are used. They are washed to rid them of liquid parts and then they are killed by subjecting them to cold and letting them macerate in physiological fluid. In the extracts of white corpuscles obtained in this way, no complements are found capable of destroying microbes. This is established, for it has been checked and counterchecked on innumerable occasions. It is not however correct to conclude on this account that the white corpuscles do not produce the complement.

To form an opinion on this much discussed topic, Levaditi and I began to study the bactericidal properties of white corpuscles. First of all we found that these cells, taken from the organism, are indeed capable of absorbing and destroying many microbes. Making use of Deneke vibrios, that resemble the microbes of Asian cholera, we were able to show quite easily their transformation into granules in the interior of the white corpuscles of guinea-pigs. This transformation, which takes place very fast with vibrios impregnated with the amboceptor or preparatory substance, implies their destruction. The white corpuscles must therefore contain in their components a substance which acts just like the complement of the humors. Now let us see how the substance behaves in fluids deprived of this bactericidal substance but having a large quantity of white corpuscles possessing the complement. One has only to keep these elements for twenty hours to discover that at the end of that time they have become completely incapable of transforming the vibrios charged with the amboceptor. The corpuscles have had time to die for the most part and in these circumstances the vibrios remain intact.

We have repeated this experiment several times with the same result, thus showing that the complement in the white corpuscles is a very fragile substance. It is beyond doubt that the long operations of washing, cooling and maceration of the white corpuscles are destructive for the complement, by and large. That is why this method must be rejected in studying the bactericidal substances in white corpuscles.

Do not think that as the action of the complement is only manifest while the white corpuscles are alive, this is purely a vital phenomenon. On the contrary it is most likely that this is a chemical action which alters according to the state of the white corpuscles. Here is an analogous example which will support this view.

The magnificent masses of living matter to be found in certain mushrooms known as "Myxomycetes" are capable, like the white corpuscles, of enveloping foreign bodies and digesting them inside the vacuoles. These are filled with acid juice which favors digestion and whose function is readily demonstrable by giving the living matter some blue litmus particles to absorb, which in a short time turn pink. Well, without killing the living protoplasm, it is enough to bruise it by pressing lightly, and the grains turn blue again. The reason is that the living matter is full of alkaline substance which straightway, at the least shock, penetrates into the juices of the vacuoles and neutralizes the acid in them. This is an example of purely chemical reaction, closely linked to the being and well-being of living matter.

It may be asked why the action of the complement is so fleeting in the white corpuscles, when it lasts much longer in the humors taken from the organism, such as blood serum. We believe the difference to lie in that the white corpuscles, over and above the complement, contain an anti-complement substance as well which prevents the action of the complement, just as the myxomycetes besides the acid juice contain alkaline substances.

Without going into more thorough analysis of this question, we can state that the white corpuscles are microscopic organisms that are more complex than they appear at first sight and that to deal with them in the mass to make extracts is almost as rough a method as squeezing whole animals, say mice or frogs, to find out their digestive powers.

As a result of research which we can do no more than outline to you in summary fashion, we still hold that the complement of the humors comes from the white corpuscles. When the white corpuscles suffer a faint attack, they only release the complement into the fluids in which they are immersed. When however the white corpuscles are subject to more serious lesion, a substance is released which neutralizes the action of the complement. We can quote as evidence to support this opinion that in the immunized organism, where the white corpuscles are intact, vibrios do not undergo the granular transformation in the humors and only take granular form in the interior of the white corpuscles.

Our plea is one of identity, for the complements contained in phagocytes and for those in blood serum. Are there, besides the complement, other substances capable of destroying microbes, substances exclusively and intimately linked to the white corpuscles? This question has as yet no ready answer, owing to the technical difficulties involved. It is likely, as appears from the research carried out by Pettersson and others, among whom we mention Max Gruber and his assistants, that substances of this kind, the endolysins of Pettersson or the leukins of Schneider, do exist in reality.

Quite apart from this intricate problem of the nature of microbicidal substances in the organism, it has been clearly shown that the power of the humors to kill infectious agents is restricted to the weakest microbes, also that the microbicidal part played by the white corpuscles and the phagocytes in general holds good for all infectious agents from which the body can have immunity.

As stated above, the bactericidal action of the complements is closely linked with another category of substances, the amboceptors of Ehrlich. They can not destroy nor damage the agents of disease. The amboceptors fasten on the agents and help the bactericidal action of the complements. The complements are localized in the phagocytes, whereas the amboceptors are to be found in the humors of the living organism and pass with ease to the fluids that accumulate round the microbes. Indubitably these are humoral substances that participate in the process of immunity. But the amboceptors are nothing else than phagocytic products excreted in the other fluid surroundings. Various researchers have established that the sources of the amboceptors are the spleen, bone marrow and lymphatic ganglia, in other words the very organs which are filled with phagocytes. It has even been shown by the experiments of Wassermann and Citron that the amboceptors arise in the places where infectious microbes have been introduced, places invaded by vast hordes of white corpuscles.

At the beginning of these investigations on the amboceptors, it was thought that the substances took part in the destruction of the microbes, but were completely alien to the system of phagocytic defense. Later it became clear that as products of the phagocytes, the amboceptors were only one of the terms of this defense.

The mechanism of the action of the amboceptors on microbes is not known in detail, not being manifest. In fact, the infectious agents impregnated with the amboceptors go on living and reproducing at the normal rate. They even keep their pathogenic power, but become

capable of undergoing the action of the complements and more prone than before to be seized and enveloped by the white corpuscles.

In the case of the most fragile microbes, such as cholera vibrios and their kind, the combined action of the amboceptor and the complement leads to the destruction of the bacteria, whether accompanied or not by the granular transformation. But the great majority of pathogenic agents give greater resistance to a mixture of these two substances, as obtained in the organism or outside it in blood serum. In this case, there can be no question of bactericidal action as it is usually understood. But the microbes, impregnated with the amboceptor and the complement, fall an easy prey to the white corpuscles. The mixture of the two substances serves most of all to prepare the phagocytosis. Because of this characteristic, it has been called opsonin by Wright and bacteriotropin by Neufeld.

Persuaded of the relative unimportance of the humors as destructive agents to infectious microbes, the followers of the humoral theories have lately fallen back on the opsonins and the bacteriotropins, considered as humoral factors well to the fore in immunity. Not being able to do any damage at all to the microbes, they only modify them in so far as their absorption by the phagocytes are facilitated. Wright, who has been largely responsible for developing this argument, insists on the subordinate role of the white corpuscles that follow blindly the opsonin lead. He even judges the progress of immunity and cure according to the opsonic strength of the blood fluid. But, insisting on the preparation of the morbid agents by the opsonins, Wright admits the virtue of the phagocytes in ridding the organism of microbes. He even goes so far as to admit the existence of a spontaneous phagocytosis, which evolves without the aid of the opsonins. The opsonins would be important, however, in making the action of the white corpuscles more speedy and more sure.

It is a priori probable that the phagocytosis, namely the swallowing and digestion of the microbes by the phagocytes, is subject to favorable influences in the organism. Is not in intestinal digestion the secretion of the pancreatic juice favored by other elements like secretin? There is thus no objection in principle to the theories of Wright and Neufeld. Only the methods on which the theories are based do tell against them. All research into opsonins and bacteriotropins has been conducted with humors and white corpuscles extracted from the organism and mixed with the microbes in glass test tubes. This method, which is very demonstrative, cannot render adequate account of the phenomena in the living body. The fate of the bactericidal theory of humors, based on experiments in vitro, should serve as a warning against placing too much trust in results obtained under these conditions. If it is true, as a great number of research workers now hold, that the opsonins and the bacteriotropins are mixtures in varying proportions of the complements and the amboceptors, one could easily understand that in the living organism things go on in quite another way than in test-tube experiments. We have already stressed the fact that the complements are linked to the phagocytes and only break away in exceptional circumstances.

In the investigations on the opsonins and bacteriotropins, investigations guided by humoral notions, on the whole only the power of the blood fluid to favor phagocytosis is regarded. The white corpuscles are taken as constant elements which can only obey the behests of the opsonins. Now the white corpuscles are living organisms, hypersensitive to external

conditions and which admit of very great variation. The least change in the salt content of the fluid which surrounds them is enough to bring about significant modification of the phagocytosis. The white corpuscles of patients attacked by different diseases show a real diminution of their vital characteristics. The work of Parvu on the cells taken from a patient suffering from myelogenous leukemia showed more than half of the white corpuscles powerless to absorb the microbes.

Faced with such facts, some scientists stress the need to study not only the opsonic property of blood fluid but also to take into account the phagocytic function of the white corpuscles themselves. This idea is justified in so far as the destruction of the microbes is the main purpose of the organism's fight against the agents of disease.

This destruction is carried out by live strong phagocytes. The absorption of the pathogenic bacteria, helped by the opsonins, is important but it is only the beginning of a series of phenomena that culminates in the digestion of the microbes within the phagocytes. In case the microbes that have been absorbed by the white globules do not die, owing to a deficiency of bactericidal substances, the organism is short on its defenses and falls victim to the infection. It can happen that highly resistant microbes, such as the spores of tetanus bacilli, can be a long while in the white corpuscles without causing the terrible illness. The moment the corpuscles suffer some deleterious influence, for example cooling or overheating, then the spores that were hitherto imprisoned are set free and do straightway produce fatal tetanic cramps.

This is why, as several doctors have already pointed out, the power of the opsonins is not enough of itself in all cases to ascertain the organism's level of resistance.

The phagocytes, subjected to influences favorable or unfavorable, have to reckon with the resistance of the agents of disease in their fight against the microbes. It can happen that the agents secrete substances which bring about deterioration in the white corpuscles to the point of dissolving them altogether. But in most instances, it is lesions which prevent the phagocytes absorbing and destroying the microbes. The substances that are directed against the phagocytes have been designated agressins by Bail. These are special poisons which attack the phagocytes in particular. In order for our defense cells to do their job properly, they must be protected against the microbial agressins. It has even been maintained that salutary phagocytosis can only take place with the aid of some preparatory action which is capable of neutralizing the agressins. This action would take its origin from elements of the body alien to the phagocytes. Series of experiments show that the white corpuscles are well fitted to absorb the agressins, without the agressins undergoing any modification. The work of Wassermann and Citron showed that the macerations of pathogenic microbes, prepared outside the organism, give a product which when introduced into the organism in quantity hinders phagocytosis. But these same microbes, generators of these agressins, are easily absorbed by the white corpuscles when the latter are in a state of reinforced activity.

The phagocytes are capable of fighting not only the agressins, I mean microbial poisons that work on the white corpuscles in particular, but even violent poisons that can kill the organism. This is a fact of prime importance in the study of immunity. After the wonderful discovery of

bacterial counterpoisons by Behring, the opinion has been voiced that the defense of the organism which enjoys immunity relies above all on the neutralizations of the toxins, which are the poisons that the microbes produce. The microbes, following neutralization, forfeit the spearhead of the attack on the organism and descend to the level of absolutely harmless entities which in turn fall easy prey to the phagocytes. Phagocytosis would thus, although acting on live microbes, be reduced to an action of entirely secondary importance.

Numerous findings, achieved with care over the last few years, clean contradict this view. It has been shown that the white corpuscles entertain no fear of microbial poisons and are well fitted to absorb them and make them harmless. This was best illustrated by work on poisons in the body of infectious microbes, going under the name of endotoxins. Besredka's work is the most conclusive in this regard. He injected the abdominal cavity of guinea-pigs with dead bacilli of typhoid fever that could not cause the infection but contained typhoid endotoxin. The animals died within twelve hours. The same injection was given to animals whose abdominal cavity contained a large number of strong white corpuscles, and these took over the microbial bodies and their endotoxin and thus saved the animal from certain death.

Bail and Weyl got analogous results using a staphylococci poison. Injected by itself, this poison kills young rabbits within a matter of hours. Injected with a certain amount of white corpuscles, this poison is inactive and the animals live on.

Such examples could be multiplied. So it seems certain that the phagocytes do ensure immunity, not only from infectious microbes but also from poisons produced by these microbes. Of all the organism's elements, the phagocytes are distinguished by their poor sensitivity to toxicity. This is so true that white corpuscles are even able to withstand poisoning by mineral poisons. When endotoxins were not so well known and when the search for bacterial poisons soluble in the organism was fraught with great difficulty, Besredka went into the question of protection afforded by the white corpuscles with regard to arsenical preparations of small solubility. He selected arsenic trisulphide, the crystals of which are absorbed and modified by the phagocytes with avidity. He found that when the abdominal cavity of guinea-pigs contained a great quantity of white corpuscles, these cells saved the animals from fatal poisoning by phagocytising the crystals of the arsenic trisulphide. Similar findings have since been established on many occasions and it is now commonly held that many toxic and medicamentous substances, introduced into the organism, are to be found in abundance in the interior of the white corpuscles. Lately Carles of Bordeaux has demonstrated the absorption of lead salts by white corpuscles. These salts were absorbed insoluble and became transparent within the phagocytes. When subjected to hydrogen sulphide vapour, however, they at once turned black. In absorbing poisons, the white corpuscles in their capacity as primitive elements comparatively non-sensitive to toxins, preserve the noble cells, such as those of the nervous system, the liver and other glands.

The sum of the very numerous facts established in the archives of science leaves no room to doubt the major part played by the phagocytic system, as the organism's main defense against the danger from infectious agents of all kinds, as well as their poisons. Where natural immunity is concerned, and man enjoys this in respect of a large number of diseases, it is a question of the phagocytes being strong enough to absorb and make the infectious microbes

harmless. It goes without saying that the phagocytic reaction is helped by every means at the organism's command.

Thus, when the microbes penetrate, the white corpuscles make use of the dilatation of the blood vessels and the nervous actions that control this, in order to reach the battle field in the shortest possible time. Every influence that can trigger off the phagocytosis is naturally brought to bear.

In immunity achieved as a result of vaccinations or subsequent to an attack of the disease, the organism shows a series of modifications. Much stress has been laid on the growth in humoral properties under these conditions. In fact the blood fluid in these cases contains considerable amounts of amboceptors and bacteriotropins (very probably identical) which prepare the microbes for phagocytosis. But, as said above, the amboceptors are products of the phagocytes. Now to secrete great quantities in the humors, the phagocytes must be modified in the organism that has acquired immunity. This might have been expected a priori but it has not been easy to prove by conclusive evidence. Pettersson had the idea of introducing white corpuscles into the organism, originating from animals that had been vaccinated against certain microbes. He found that these elements do give real protection against doses of infectious microbes that are fatal several times over. On the other hand, the white corpuscles of an organism which does not have immunity are powerless to produce this result.

Salimbeni, in view of the outstanding import of this, began a series of experiments at the Pasteur Institute, with the aim of checking Pettersson's findings. Using a method that allowed of great accuracy, he was able to confirm these findings and take them further. He showed that the white corpuscles of the immunized organism are a true source of protective substances, and that at a time when the blood fluid does not yet show any modification. In spite of successive washings, the phagocytes still ensured immunity. In the course of his research, Salimbeni proved that at the moment when the humors have already lost their protective powers altogether, the organism is still refractory and resists fatal doses of infectious microbes. This fact, together with other supporting evidence, leads to a conclusion of the greatest importance. Namely, that even in acquired immunity, the properties of the cells take pride of place over the humoral properties.

At this point, it may seem paradoxical that in spite of the serious modifications that follow acquired immunity, the white corpuscles show no augmentation of their function which may strictly be termed phagocytic. They absorb the infectious agents to the same extent as the white corpuscles taken from a normal organism and put into contact with the humors of the immunized organism. Ever since the first experiments of Denys and Leclef, those concerned have stressed the importance of this finding. It must not be forgotten that these experiments were conducted with white corpuscles taken from the organism and studied in vitro. In spite of all that has been said on this score, the objection is valid. Comparison is drawn between phagocytosis of the white corpuscles of an organism that has been subjected during weeks and months to injections of vaccine and all the while kept captive, and the white corpuscles of a fresh organism which has never been under attack. The conditions, as may be seen, are far from identical.

Even were it soundly established that the phagocytes in acquired immunity do not undergo any modification, to their power of absorbing microbes, this result would not in any way invalidate the general fact of augmentation in the defensive power of the phagocytic system. It need only be admitted in this instance that just as for acquired immunity there is no augmentation found in the production of the complements, so there is no augmentation in the property of enveloping. The strengthening of the defense would then be reduced to overproduction by the phagocytes of substances that prepare the way for phagocytosis.

The total of phenomena observed in immunity thus reduces to a series of biological acts, for example the sensitivity of phagocytes, their active movements directed to areas imperiled by the microbes, and a series of chemical and physical acts which bring about the destruction and the digestion of the infectious agents. Since a dozen years, under the impulse provided by the theories of Ehrlich, many men of science have tried hard to lay bare the inner mechanism of the phenomena of immunity. Ehrlich himself held that the amboceptors, which abound in acquired immunity, combine in determined proportions with the molecules of the complements on the one hand and with those of the microbes, i.e. their receptors on the other. Many field-workers, led by Bordet, fight this theory. According to them, the amboceptors are unworthy of the name, for they are not the chemical go-between of the complements and the microbes, but act on these like the mordant in tissue dyeing. Bordet also calls amboceptors by the name of sensitizing substances, on account of their property to facilitate the action of the complements on the microbes. The whole phenomenon falls in his eyes into the category of molecular absorption in varying extents.

The polemic on these two theories has been going on ten years. The problem of the inner mechanism of immunity is so delicate and complicated that it is not yet definitely resolved. It must however be said that many research workers find it fashionable to support the idea that the action of the organism on microbes is outside the picture of chemical phenomena strictly so-called, and is rather in the domain of the physical actions of the colloids, some of which spring from the microbes while others belong to the organism. Analogies are sought between substances that are observed in immunity and the colloids. Some are not far from saying that the complements are lipoids, analogous to those that come in to the constitution of animal organs.

All this research promises results of prime importance in the more or less near future. At the moment, what it amounts to is no more than incursions into a field thick with thorny problems. The place of the phagocytic system in immunity has however emerged from the stage of theory and is now doctrinal.

It is time to ask now if the notions acquired from so many years' work and discussion yield practical application in medicine. This general law that in all cases of immunity the phagocytic reaction is pronounced, leads one to conclude that the degree of phagocytosis can be used in medical prognosis. From the beginning of our research on phagocytosis, we became convinced that the more the microbes were absorbed by the white corpuscles, then the more chance the animal had of surviving and making a complete recovery. Swiss veterinary expert, Zschokke, was the first to make use of this rule in the struggle against infectious

mammitis in cows, which is an epizootic that causes serious deterioration in milk. He was able to show that plentiful phagocytosis of streptococci, which are the disease bearers of this sickness, is a good sign that all is going well. The fate of cows suffering from "gelber galt", as mammitis is locally called, depends on the extent of phagocytosis. When this is insignificant or nil, the cows are written off as no longer productive of good milk. A whole system has been built up to determine the degree of phagocytosis and this is confirmed by findings on slaughtered animals. Although in most instances, the extent of the phagocytosis gave a precise indication, examples have been known of cows which did not recover although the majority of the streptococci was contained within the white corpuscles. These exceptions in turn led to new field-work on the part of Vrijburg. As was to be expected according to phagocytosis theory, for the organism to triumph over the infectious microbes, these must not only be absorbed by the white corpuscles but also utterly destroyed. There are cases where the streptococci of mammitis, after absorption by the phagocytes, demolish the cells and finish by being free to carry on their deadly work. To arrive at sound prognosis, the extent of the phagocytosis must be measured and the state of the phagocytes with the microbes within them must be known too.

This example of contagious mammitis should admonish those who think it enough to determine the opsonic strength to be able to judge how an illness or indeed immunity is faring.

In other diseases brought on by streptococci, the degree of the phagocytosis can also serve as a prognostic. Professor Bumm in Berlin uses this method to prognosticate puerperal fever. Strong phagocytosis indicates speedy recovery, while minimal or slight phagocytosis means the worst is to be feared.

In the treatment of illness by Dr. Wright's vaccinothrapy, the phagocytosis shows the opsonic strength of the blood. It is thus a guide to the doctor. We said above that this method was coming to be joined by that of determination of the property of phagocytes, independently of the opsonic action in itself. For some time phagocytosis has been used with success in the diagnosis of certain infectious diseases.

Among the practical applications of the doctrine of phagocytosis mention must be made of the use in surgery of substances capable of bringing a large quantity of white corpuscles to areas under operation and open to infection. There are already surgeons in France and in Germany, who introduce into the abdominal cavity or under the skin of their patients either warmed blood serum or nucleic acid or other substance, with the object of bringing to the scene a protective army of phagocytes to ward the microbes off. The results achieved are so encouraging that it is possible to predict new progress in the approach to the dressing of wounds. At the opening of the new era in surgery, only the microbe was taken into account and the patients were soused in antiseptics. It was soon seen that these are poisons that spell danger to the organism under treatment. Antiseptics gave way to aseptics. Now it is known that phagocytosis is a valuable force in the organism's defenses, an attempt is being made to modify surgical methods by the adjunct of means that reinforce the number of the phagocytes.

Of the therapeutic methods that have emerged latterly, we note the process of Professor Bier. This consists in the systematic application of cupping-glasses and rubber strips to augment the venous stasis round abscesses, furuncles and similar afflictions of many kinds. Cure is often achieved by this means with a rapidity that is little short of surprising. It has been asked what caused such success. Modern methods of research at their most refined have been used. The contradictions have not been entirely removed. But it is generally held that the phagocytosis is an important element in cure effected by the Bier method. The application of cupping-glasses and bands causes venous stasis and thus an edema is formed round the injured area. At the same time, a large number of white corpuscles come to the spot, and these serve to strengthen the phagocytosis. In a very recent treatise on this subject, the Japanese Dr. Schimodaira, working in a European laboratory and with no particular love of the phagocytic theory, has nevertheless been forced to admit that augmenting the phagocytic reaction in the use of the Bier method is one of the main factors effecting cure.

It is small wonder after so much evidence has been given on the valuable part played by the phagocytes, that research should concentrate on the conditions capable of strengthening phagocytic reaction. A number of works has recently been published on this topic. Among the substances that activate phagocytosis, mention can be made of quinine, a medicine much loved by medical practitioners. Grünspan's research shows that weak solutions of two milligrams per hundred raise the power of phagocytosis to a marked degree, while solutions fifty times stronger give the opposite result. Neisser and Guerrini have studied a whole series of substances that stimulate phagocytic activity, among which they make especial reference to certain solutions of peptones. The chapter on stimulins that we opened a long time ago and that had lain forgotten has recently been put back on the map again. All means are used to augment the phagocytic reaction to ensure cure and immunity. How different by far from the ideas that were once sovereign in medicine. I remember forty years ago the famous Helmholtz having learned from Cohnheim that the pus corpuscles in inflammation come from the white corpuscles in the blood, taught, in accordance with the then current theories, that the accumulation of such elements constituted a danger to the organism, a danger that must be met by doses of quinine, capable of paralyzing the movements of the white corpuscles. It is enough to compare this point of view with the actual concept of the benign role of the inflammatory reaction in general and of the phagocytic reaction in particular, to gather how far we have come.

The theory of phagocytes, laid down more than twenty-five years ago, has come under heavy fire on all sides. It is only of late that it has won recognition from the well-informed in all lands, and it is only as it were yesterday that it has begun to have practical use. We have thus the right to hope that for the future medicine will find more than one way to bring phagocytosis into play to the benefit of health.

I have attempted to outline the present state of a subject that may serve as an example of the useful purpose to be served by purely theoretical research. The study of the origin of the digestive organs in the lower animals, since long disappeared, has opened up the field little by little, leading to a new concept of immunity, to the quest for methods of fighting infection and ensuring resistance and recovery, of the organism.

In awarding me a prize for my research on immunity, the Nobel Committee has chosen to honor me for all my work done over twenty-six years, and in part carried out by my many pupils at the Pasteur Institute.

I express my deepest thanks to the Committee for this great distinction which gives me the greatest joy any savant can wish for. I have however one fear. Namely that the Committee is esteeming my work beyond its true worth. I take heart from the thought that it was the intention of the generous founder Alfred Nobel to reward men of learning who give their lives to knowledge without deriving any benefit from its practical applications.

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