LECTURE
ON
PHAGOCYTOSIS AND IMMUNITY.

Delivered at the INSTITUT PASTEUR, December 29th, 1890.

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[Translated from the Original Manuscript by J. G. ADAMI, M.A., M.B.Cantab., John Lucas Walker Student in Pathology in the University of Cambridge.]

It is not possible to study the bacteriology of disease without noticing that, while in many cases the invading micro-organisms are to be found solely in the fluids of the body, in not a few affections they present themselves in the interior of certain cells, and this either partially—some being within the cells, others free in the blood plasma and the lymph that bathes the various tissues—or exclusively, all the bacteria that are visible being intracellular. Many of the facts bearing upon the terms of this relationship between tissue cell and micro-organism are now well known, yet it is worth while to recapitulate the more important, in order to show that from them it is possible to gain a general law, and what is more, that from a study of such facts some insight may be gained into the phenomena of immunity.

It may, in the first place, be postulated that, whenever a micro-organism is discoverable within a cell, its passage thither has been by means of protoplasmic movements, of amœboid movements either on the part of the microbe, or of the cell itself. The first alternative is the rarer, although it certainly exists, and of this the malarial parasite affords an excellent example; for here in the amœboid stage of its existence the hæmatozoön makes its way into the interior of a cell that possesses no active movements of its own, namely, the red blood corpuscle, and from the substance of this corpuscle the parasite gains its nourishment. Other sporozoa furnish instances almost equally good. More commonly, however, as in the case of all bacteria, where we have to deal with micro-organisms which, even when mobile, are destitute of protoplasmic appendages, it is the cells which play the active part; certain cells include the parasites. Of such, the amœbiform leucocyte of the blood and lymph is the most typical example, capable, as it is, of sending out pseudopodia in all directions, while a closely-allied form is the cell of the splenic pulp. But there are also cells, as, for instance, those forming the endothelial lining of the vessels, which are very definitely fixed, which, nevertheless, can give off protoplasmic processes from their free surface, and so capture and include bacteria.

All these may be spoken of as *Phagocytes*, and may be divided into the two broad groups of *fixed* phagocytes (endothelial cells, etc.) and *free* (leucocytes); not that the terms "phagocyte" and "leucocyte" are synonymous, for of the latter three main forms may be distinguished, of which one is practically immobile and never takes up bacteria. This is the *lymphocyte*, characterised by its relatively small size, its large single nucleus, and the small amount of surrounding protoplasm. The two remaining (phagocytic) forms are (1) the large uninuclear leucocyte, whose prominent nucleus is at times lobed or reniform, which stains well with aniline dyes and possesses much protoplasm and active amœboid movements—the *macrophage*—and (2) the *microphage*, a small form, also staining well, but either multinuclear or with one nucleus in the process of breaking up. (See Fig. 3.) If now we compare the endothelial cells with these, it is evident that their properties connect them closely with the macrophage; and, in fact, there is now little or no doubt that a very large proportion of the macrophages are of endothelial origin.

Leaving aside the subject of amœboid microbes and their life within animal cells, it is to the phagocytes and their relation to the bacteria that I wish specially to draw your attention.

Taking as wide a view as possible of this relationship, we can first determine that *the more malignant the micro-organism the rarer is its presence within the phagocyte.* Thus in those which of all diseases are the most rapidly fatal—in chicken-cholera affecting birds and rabbits, in hog-cholera ("choléra des porcs") given to pigeons and rabbits, in the anthrax of mice and other specially sensitive animals, in the "septicémie vibrionienne"[1] of guinea-pigs and birds, and in yet other diseases of peculiarly swift course—the corresponding bacteria are only very exceptionally to be found within the cells, but remain free in the neighbourhood of their introduction, and thence invade the blood. For all the above-mentioned diseases are not localised, but, on the contrary, present the characters of general acute septicæmia, causing death within twenty to thirty-six hours, or, in certain cases, even within six hours.

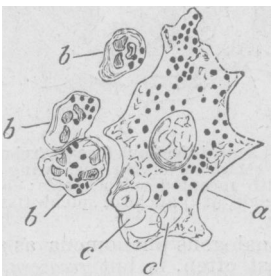

Fig. 1.—Staphylococcus pyogenes aureus contained in epithelial cell *a*, and leucocytes (microphages) *b b* of alveoli of lung of rabbit (Laehr), *c c* vacuoles.

And when we pass to those diseases in which the bacteria are to be found either in part or almost wholly within the phagocytes, the same law still applies; for in such cases the disease has lost its suddenness, tending to have a slower course, or, indeed, to be of a chronic nature. Even in those affections in which an acute course is accompanied by considerable phagocytosis, the fatal termination is far from occurring at the same early period as in the diseases recorded above. Thus mouse septicæmia, characterised as it is by frequent intracellular bacteria, has a duration in the mouse two and a half times as long as that of anthrax in the same animal. But in general a well-marked phagocytosis is associated with diseases presenting an essentially chronic development; it is in affections such as tuberculosis, leprosy, rhinoscleroma, glanders, that the specific bacteria are most readily taken up by the phagocytes; it is here that at the seat of the disease we meet with innumerable macrophages—epithelioid cells in which lie the individual micro-organisms.

Further if we consider the phenomena associated with the resolution of an infectious disease, this inverse relationship between the malignancy of the malady and the occurrence of phagocytosis is, if possible, yet more clearly demonstrated. Notice, for instance, what obtains during the progress of relapsing fever, a malady still fairly common in Russia and other Sclavonic countries, and one which, while presenting many difficulties to the bacteriologist in that the specific spirochaete has so far resisted cultivation, and in that it cannot be communicated to the ordinary animals of the laboratory, is nevertheless in many respects not ill adapted for our present purpose. Here, during the sudden access of the fever, the spirilla are present in the blood in enormous numbers, they all are free in the plasma, and not a single intracellular spirillum is to be met with. During the apyretic stage (and in the monkey this is, at the same time, the stage of resolution) not a single free spirillum is discoverable in the blood, while the phagocytes of the spleen contain the microbes. The like phenomena repeat themselves in all those cases where it is possible to follow the fate of the micro-organisms of acute disease during the stage of recovery. Thus rats and pigeons very frequently survive an attack of anthrax, and, where this

[1] The disease produced by a micro-organism, which in appearance and methods of growth is curiously like Koch's cholera spirillum. Gamaleïa, its discoverer, named it "Vibrio Metschnikovi;" and as such, in place of M. Metschnikoff's own vaguer "septicæmic vibrio," it will be spoken of in later reference to its properties. The disease it originates will be spoken of as "vibrionic septicæmia."—Trans.

occurs, the bacteria, which at the commencement of the disease were for the most part free, now, during resolution, are for the most part included within leucocytes and splenic phagocytes.

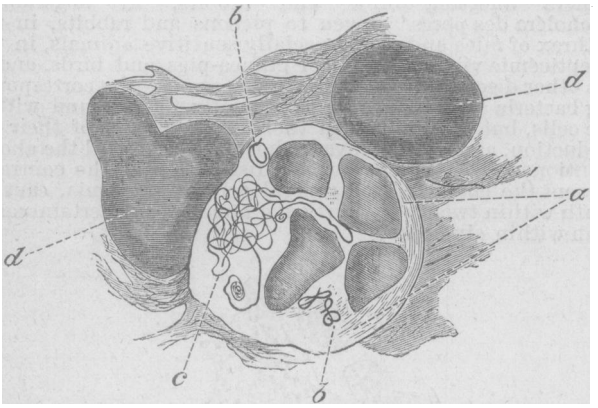

Fig. 2.—Resolution of acute infectious disease (relapsing fever), spleen pulp of monkey (Macacus erythr.), showing (*a*) a microphage, multinuclear, with incepted spirochaetes; (*b*) solitary, and (*c*) forming dense tangle, (*d d*) nuclei of splenic tissue (Zeiss, $\frac{1}{12}$ ocular 4; × 1515 diam.).

Nor is this all; analogous phenomena as a rule attend immunity, which, most often, is but *recovery in operation from the very onset of a disease*. The more closely one studies this condition of immunity, the more is one led to the conviction that immunity and recovery are very intimately connected, that one can pass by slight gradations from the resolution of disease to the production of immunity. So it is that, in inoculating refractory animals with the microbe to whose action they have been rendered immune, it is found that the parasite *begins to develop, but that from the onset a reaction on the part of the organism shows itself*, accompanied by a considerable emigration of leucocytes which soon include the bacteria in great numbers.

This relationship of phagocytosis to acquired immunity is in the highest degree instructive. Where a given species of animal is specially sensitive to the onslaught of one or other micro-organism, there, during the course of the disease, the phagocytes are inoperative, including none, or almost none, of the bacteria. On the other hand, when by previous vaccination these animals have been rendered refractory, their phagocytes have acquired the property of including the same bacteria. As an example of this I may cite the action of the bacillus of anthrax and of the vibrio

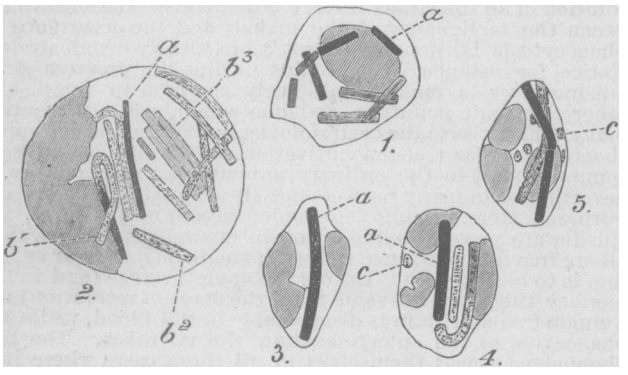

Fig. 3.—Anthrax of pigeon (an animal but slightly susceptible to the disease) to show stages of destruction of bacilli by phagocytes. *1* and *2*, macrophages: *1*, from exudation from eye of refractory bird; *2*, from muscle of region of inoculation of bird that succumbed; *3*, *4*, *5*, microphages—all from eye twenty-seven hours after inoculation; *a*, *a*, unaltered bacilli; b^1 b^2 b^3, bacilli becoming more and more degenerated and indistinct; *c c*, *débris* of bacilli (Zeiss $\frac{1}{12}$, ocular 3).

Metschnikovi. In ordinary rabbits the development of anthrax is only followed by a very feeble phagocytosis, while in vaccinated rabbits this phagocytosis is very extensive. Corresponding, but yet more strongly marked, differences are to be made out between the unvaccinated guinea-pig—an animal most readily affected by the vibrionic septicæmia—and the guinea-pig vaccinated against the same; after inoculation with the vibrio Metschnikovi, none of the vibrios are to be found in the cells of the former, in the latter the phagocytes are simply replete with the microbes.

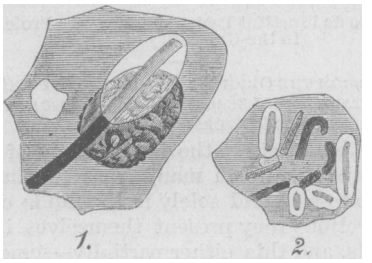

Fig. 4.—Phagocytes, macrophage and microphage, to show stages of digestion and destruction of bacilli, from spleen and eye respectively of white rat with anthrax. In *1* part of the bacillus is unaffected, but a vacuole has formed around the other part, which further has now lost the power of taking the stain. In *2*, various stages are seen, the bacilli passing through the granular badly staining, to the vacuolated unstained, until finally but faint "shadows" are observable (Zeiss $\frac{1}{12}$, oc. 3).

The facts enumerated thus far would seem to prove that there exists a certain antagonism between the microbes and the phagocytes, and this view is confirmed by the fact that in general the microbes find the interior of the phagocytes an unfavourable medium for their development and con-

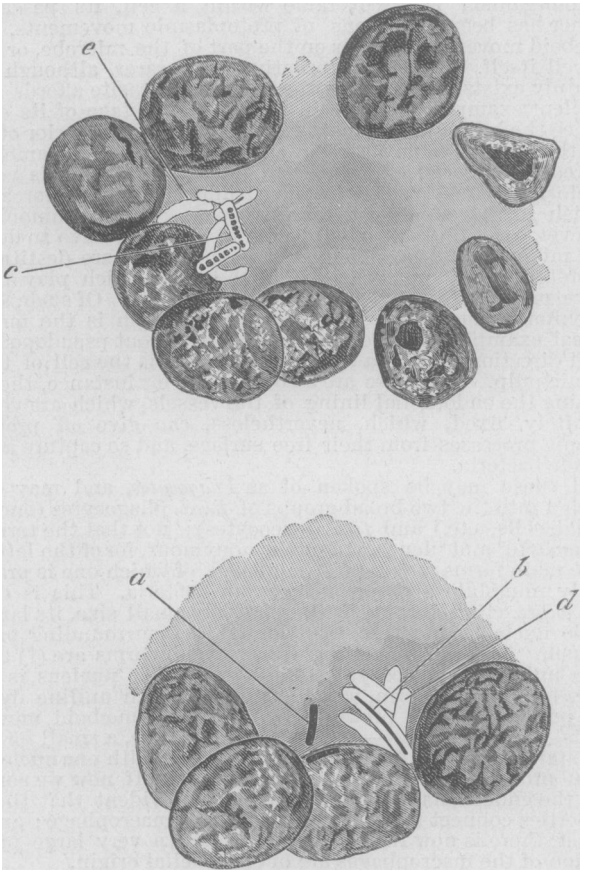

Fig. 5.—Two giant cells seen under high magnification (× 1515 diam.) from a rodent, the spermophile, inoculated with tuberculosis, to show stages in the destruction of the bacilli. *a*, unaltered bacillus; *b*, bacillus staining badly, and with greatly thickened capsule; *c*, bacillus granular and breaking up; *d*, *e*, "shadows."

tinued existence. Very often it is possible to determine absolutely that the parasites are killed within the phagocytes; after inoculating refractory animals with bacteria, an afflux of white corpuscles towards the region of inoculation, followed by the inclusion of the bacteria and by their death, is seen to occur. These stages can be well followed where the anthrax bacilli are taken into the phagocytes of animals that are, or have been rendered, immune. They occur also with a long series of other micro-organisms studied in this connection, and among others in the case of the tubercle bacillus invading animals that are more or less resistant. The giant cells of tuberculosis are, in fact, huge multinuclear phagocytes; and here the intracellular destruction of the bacilli is the more clearly demonstrable inasmuch as the micro-organisms exhibit such very evident signs of degeneration; the bacilli swell, their enveloping membrane becomes much thickened and highly refractive, and in time the contents lose their power of fixing the staining material, so that eventually nothing is left but slightly yellowish forms, recalling in proportions and position the enlarged bacilli, and these shadowy bodies unite into small masses of an amber-like appearance. Analogous transformations never being observable outside the phagocytes—that is to say, either in cultures or in caseating masses—these changes may well be regarded as due to a specific action upon the part of the giant cells.

The broad fact that the invasion of the organism by microbes most often induces, on the one hand, an inflammatory reaction with its associated emigration of leucocytes, and that, on the other hand, the phagocytes are capable of including and destroying the invaders, leads us to admit that *the afflux of phagocytes to the invaded region, and their bactericidal properties, are mechanisms which serve to ward off bacterial attack and to maintain the integrity of the organism.* Where the phagocytes do not, either immediately or eventually, intervene, but leave the field free to the microbes, these last multiply without hindrance, and succeed in killing the animal within, it may be, an excessively short period. Thus the micro-organism of hog cholera, which is left quite untouched, kills the pigeon in the course of a few hours—often within five hours after inoculation: chicken cholera kills not only pigeons but also rabbits in an equally short period. In other diseases in which the phagocytes appear upon the scene in relatively large numbers, and even include the micro-organisms, the latter gain the day whenever and wherever the phagocytes are incapable of destroying them or of preventing their growth.

This manifest bactericidal action is to be compared with the phenomena of intracellular digestion characteristic of amœboid cells in general, and of leucocytes and other microbic phagocytes in particular. These cells have the power of digesting with ease red corpuscles and other organised elements; just as have the amœbæ proper, and other protozoa. Among these last are many which have been found to include and transform bacteria in exactly the same way as do the phagocytes of the higher animal.

Now, in determining the intervention or non-intervention of the leucocytes in this war between the organism and the bacteria, a very great part is played by the sensitiveness of these cells to external influences, and especially to the chemical composition of their environment. The leucocytes are powerfully attracted by many micro-organisms and the resultants of their growth, and as powerfully repelled by others and their resultants, or, as it is expressed, they have a *positive chemiotaxis* for certain microbes, a *negative chemiotaxis* for others. The existence of these chemiotactic properties has been so clearly proved of late by the researches of Leber, Massart and Bordet, and Gabritschewski that I need not enter into a fuller explanation of the subject here. Where *negative* chemiotaxis manifests itself, there, being shunned by the white corpuscles, the parasites freely propagate themselves and induce the death of their host. Nevertheless, this chemiotaxis is not immutable, and the cells can become accustomed to substances from which they shrank at first—a negative may thus be transformed into a positive chemiotactic state. Such obtains in acquired immunity; the cells which, in the unvaccinated animal never included the bacteria, now, in the vaccinated, take them up readily.

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There is not a single portion of the theory which I have just expounded but has encountered a lively opposition. Even the fundamental fact that the phagocytes are capable of including the microbes has had doubts thrown upon it; it has been held that the latter insinuate themselves into the former. Only after successive series of observations upon the phagocytes and the living microbes has it been proved that assuredly it is the phagocytes which by the aid of their pseudopodia themselves include the micro-organisms. The observer can see the whole process in the case of immobile bacilli, can see the leucocyte approach, send out pseudopodia, and gradually include the individual bacillus. Or conversely in cases of negative chemiotaxis, one can, in blood taken from the monkey during the access of relapsing fever, observe the actively moving spirilla come into contact with a leucocyte, and even become attached by one end to its surface; yet, however active the movement, one never finds that the spirillum succeeds in piercing the surface and gaining an entrance. If it be suggested that this entry may take place in consequence of the force of active growth and elongation of bacilli, then apart from the fact that here but one set of cases is embraced, it can be determined that this force is too feeble, it can be seen that, during the active growth of the anthrax organism in the blood, the elongating chains of bacilli curve in and out between the corpuscles, but never penetrate the cells.

From another side the objection has been formulated that in many cases the organism gets rid of its invaders without the aid of the phagocytes. According to those who support this objection, this happens in the anthrax of pigeons (Czaplewski), and of refractory rats (Behring, Franck), in symptomatic anthrax of various refractory animals (Rogowicz), and in the septicæmia of vaccinated guinea-pigs due to the vibrio Metschnikovi (R. Pfeiffer). A re-examination of the cases here adduced has, however, shown that in each a very considerable phagocytosis can be proved, and that the negative results of the above observers have been due to insufficient methods of observation.

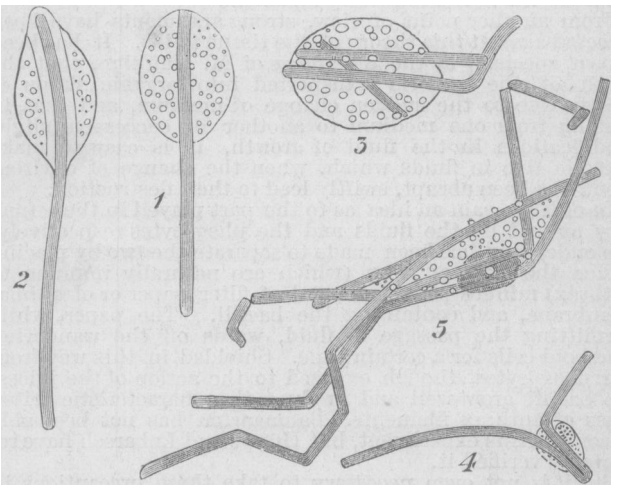

Fig. 6.—Bacilli of anthrax growing out of phagocytes that have been killed by the addition of bouillon to the drop of exudation in which they were contained from the refractory pigeon. *1* and *2*, stages in growth of same bacillus; *2*, $\frac{3}{4}$ were later than *1* (Zeiss F, oc. 4, for 1, 2, 3, D × oc. 5 for 4, $\frac{1}{18}$ and oc. 2 for 5).

While accepting that the phagocytes do truly absorb the micro-organisms, other opponents of the theory have urged that these cells are only capable of including micro-organisms already killed by other means, and that living microbes are solely to be found within the cells in those cases where there has been a fatal ending—in tuberculosis, mouse septicæmia, and so on. Against this may be brought the fact determined by Lubarsch, that the phagocytes of several animals refractory to anthrax take up living bacilli that have been injected with greater eagerness than they include those which have been killed before injection. But further, this objection may be disposed of by direct observation of bacteria undergoing development from within the interior of phagocytes after the

latter have been destroyed by a substance which is at the same time a favourable medium for bacterial growth, as, for instance, beef broth. Such observations have been made upon pigeons rendered immune to anthrax.

During the last year or two great stress has been laid upon the fact that the bodily humours themselves possess most marked bactericidal properties, and, in fact, against the theory of phagocytosis has been brought another based upon this power of the humours to destroy the micro-organisms. Observer after observer has remarked that in blood plasma, defibrinated blood, blood serum, and in the blood as a whole, in the removed aqueous humour and other fluids and exudations of the body, many species of bacteria perish after a longer or shorter interval, and forthwith an endeavour has been made to find in these facts some elucidation of the phenomena of immunity. Yet the more deeply one examines into the question, the more one is convinced that no relationship exists between the two. Thus it happens often that the bactericidal property is more developed in susceptible species than in refractory; so with regard to the anthrax bacilli, in the very sensitive rabbit the bactericidal properties of the humours are more pronounced than they are in the refractory dog; and Behring and Nissen, the two who almost simultaneously first drew our attention to these phenomena, in their combined research recently published, admit that, as against the bacteria of anthrax, pneumonia, and diphtheria, this bactericidal property exists to the same degree in the juices of animals of the same species, whether they be susceptible or have been rendered immune. Often, again, it has been determined that the blood removed from the organism has a greater power of destroying bacteria than it has within the organism. A small quantity of blood withdrawn from the body will, in certain instances, kill a mass of bacilli greater than that which, injected into the circulation, would inevitably cause death. Evidently, therefore, in this bactericidal influence, extravascular phenomena enact an important *rôle*, —phenomena, that is, which have no connection with what occurs in the living refractory organism.

From another point of view, strong arguments have been directed against this theory of the tissue fluids. It has been shown, specially by the researches of M. Haffkine, that the death of the bacteria transported into organic fluids is largely due to the sudden change of medium, and that in passing from one medium to another by successive slight modifications in the fluid of growth, it is easy to make bacteria live in fluids which, when the change of environment has been abrupt, swiftly lead to their destruction.

In order to gain an idea as to the part played in the refractory animal by the fluids and the phagocytes respectively, the endeavour has been made to separate the two by placing under the skin of frogs (which are naturally immune to anthrax) minute packets formed of filter paper or of animal membrane, and containing the bacilli. The paper, while permitting the passage of fluid, wards off the wandering amœboid cells for a certain time. Shielded in this way from the phagocytes, though exposed to the action of the juices, the bacilli grow well and produce the characteristic felted mass of anthrax filaments. Baumgarten has not been able to confirm this experiment, but Hüppe and Lubarsch have repeatedly verified it.

But it is not even necessary to take these precautions in order to assure oneself that anthrax spores germinate in the juices of refractory animals. Recently, for instance, M. Trapeznikoff has found that when these spores are injected into the dorsal lymph sac of the frog, they constantly tend to develop into bacilli whose further growth is stopped by the phagocytes, which include them, along with such spores as have not had time to germinate. Eventually the bacilli so absorbed are digested by their hosts, while the included spores remain intact, although incapable of giving birth to bacilli for so long a time as the phagocytes remain alive. And I might adduce other similar cases. Such a comparative examination proves that in the living body the bactericidal property resides in the phagocytes, and not in the fluids.

Still it may be urged that possibly these cells, which can thus devour and destroy the living microbes, are only in a position to attack bacteria whose virulence has already been lessened by other means. Were this so, the microbes present in a refractory organism should behave, not like parasites, but as simple inoffensive saprophytes. Hence these microbes—powerless to produce upon a refractory soil the toxic substances which render them pathogenic and dangerous—should easily be included and destroyed, so that, according to this hypothesis, which has frequently been brought forward, the phagocytes play a purely secondary and dependent part, waiting until the microbes are weakened before they seize upon them. In favour of this view the fact has been cited that certain micro-organisms cultivated in the blood or serum of vaccinated animals become attenuated, so that they no longer induce a fatal disease. The bacillus anthracis grown in the blood of vaccinated sheep no longer kills rabbits, and, according to Roger, the streptococcus erysipelatosus grown in the blood of vaccinated rabbits only occasions a slight and passing disturbance in susceptible members of the same species. But here again we are dealing with fluids withdrawn from the body, and so modified in various ways. Let us make an observation more strictly to the point. Take, for instance, a rabbit vaccinated against anthrax and inoculate it with anthrax bacilli, thus allowing these to exist directly within the refractory organism. Such bacilli as are not destroyed preserve their virulence for a sufficiently long period, and it is possible to kill a guinea-pig with a drop of exudation taken from the region of injection thirty hours after subcutaneous inoculation, eight days after inoculation into the anterior chamber of the eye. A sojourn of so long duration within the vaccinated organism, then, has not deprived the microbes of their virulence, although twenty-four hours suffices to completely attenuate the bacilli cultivated in the removed blood of vaccinated sheep.

Years ago, it was established in M. Pasteur's laboratory that the refractory organism, instead of being an unfavourable soil for the preservation of virulence, tends the rather to reinforce this property. To exalt the virulence of an attenuated micro-organism, one always employs, not animals very susceptible to the specific disease, but those which are slightly susceptible, or it may be, under many circumstances, refractory. In this manner, the most active anthrax virus has usually been obtained by passage through birds, notably fowls; the greatest virulence of chicken cholera was gained by passage through the vaccinated cock, and quite recently M. Malm has shown that passage of the anthrax bacillus through the organisms of dogs, which of all mammals are the most refractory in this respect, increases its virulence in a most remarkable manner, so that the general law may be laid down that an organism which is but slightly susceptible or is refractory is able not only to preserve, but even to exalt, the virulence of bacteria. The principal argument in favour of the hypothesis, that pathogenic micro-organisms become simple inoffensive saphrophytes when they find themselves in a refractory region, loses therefore its *raison d'être*.

M. Bouchard, in his objection to the theory of phagocytosis, may be regarded as introducing but a modification of this hypothesis. He holds that pathogenic bacteria placed under favourable conditions give rise to substances which hinder the inflammatory process, and that only when these inhibitory substances are inadequately represented do the cells intervene. When, therefore, the organism rendered refractory by vaccination becomes an unfavourable soil for the production of these inhibitory bodies, the bacteria can no longer prevent the inflammatory reaction; free emigration of the leucocytes ensues, these cells seize upon the impotent microbes, and put a stop to their further growth. In this theory, the part played by the phagocytes is again secondary, depending upon a dearth of anti-inflammatory substance.

If the theory could be accepted in certain cases, it is nevertheless inapplicable as a general rule. In all those affections which are characterised by the absence of leucocytes upon the field of battle there is certainly no lack of inflammation. The very reverse obtains. In anthrax affecting small mammals, just as in the vibrionic septicæmia of pigeons and guinea-pigs and other analogous diseases, we find that there is a very distinct dilatation of the vessels, accompanied by great exudation; the inflammatory reaction is well marked, nothing is wanting save the determination of the white corpuscles. Or employing yet further that affection, which is, as it were, the touchstone of the bacteriologist, a still clearer proof of our contention is to be gained, if we inoculate a

rabbit on the one ear with a small quantity of virulent, on the other with a like quantity of attenuated, anthrax virus. In the course of a few hours the external signs of inflammation are far more conspicuous in the former; the vessels are greatly enlarged, and there is literally a huge exudation of clear serous fluid into the part; in the latter the external signs are less prominent, but examination of the seat of inoculation shows it to be packed with leucocytes. Consequently, the phenomenon we are discussing is to be explained not by an absence of the inflammatory process, but much more satisfactorily by a negative chemiotaxis of the leucocytes, which, instead of being attracted by the bacterial products, are repelled; where the animal is vaccinated or refractory a much slighter inflammation is sufficient to produce an abundant emigration of the leucocytes.

During the last few days Behring has brought forward another view which would explain immunity in a wholly different way. According to him the bacteria can live and even preserve their virulence in the refractory organism, but the *toxines* excreted by them now undergo a modification so as to be rendered completely inoffensive for the animal. And to this "toxicide property" of the organism is to be attributed the essential quality of the immune state. It is impossible to pronounce upon the arguments that have led up to this theory, for as yet they have not been circumstantially set forth, but already one can declare that such a theory is in no wise applicable to the phenomena of immunity in general. In three diseases remarkable for their pronounced toxic character—vibrionic septicæmia, pyocyanic disease, and hog cholera affecting the rabbit—as shown by the experiments of Charrin, Gamaleïa, and Selander, the toxines are so little attacked by the refractory organism that the same quantity of these substances (freed from bacteria) suffices to kill an animal very susceptible to one or other disease, and an animal vaccinated against it and thus completely immune. So too non-fatal doses of these toxines produce in animals of the two categories the same febrile and inflammatory reactions. The proof is clear that there is no special destruction of toxines in the refractory animal, and that the "toxicide property," if it exists, is not one whit more developed after vaccination than before.

Passing in review all these counter theories we see that each of them can only be applied to a certain number of facts; in some an attenuating or even bactericidal influence of the juices is relied upon, in others an anti-inflammatory action; in yet others a toxicide property. Still the phagocytic reaction is the only constant in all those cases of immunity and recovery that have as yet been sufficiently studied, and while certain of the factors mentioned (the attenuating and toxicide properties) do not in the least touch upon the continued existence or otherwise of the micro-organism, the bactericidal power of the phagocyte puts an end to the parasite itself, and thus at a given moment prevents further manifestation of its virulence, or preserves the animal attacked at a time when the toxicide properties would be found wanting, and the microbe remaining alive would consequently gain the upper hand.

But while thus placing before you the important part played by the phagocytes, I do not wish it to be thought that these cells are unaided in their contest by other defensive means possessed by the organism. This is far from being my view. Thus, in the febrile reaction, we see a puissant auxiliary very definitely favouring the work of the phagocytes. This febrile reaction has only to be inhibited—as was done by M. Pasteur in the anthrax of fowls—and animals naturally refractory to the affection succumb to the ravages of the bacilli. It is not possible at the present time to state fully and accurately all these influences which are associated in aiding phagocytic action, but already, we have the right to maintain that *in the property of its amœboid cells to include and to destroy micro-organisms, the animal body possesses a formidable means of resistance and defence against these infectious agents.*

A MEETING was recently held at the Academy of Medicine, New York, for the purpose of organising an American Electro-Therapeutic Association. The committee consists of Drs. G. Belton Massey, A. H. Goelet, and H. R. Bigelow.

A CASE OF TACHYCARDIA OR RAPID HEART SUCCESSFULLY TREATED BY ELECTRICITY AND LARGE DOSES OF BELLADONNA.

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IN July, 1890, I was asked by Dr. Farquharson, of Newcastle, to see with him in consultation a young man, aged 28—a nervous, anxious-looking and emaciated man, who was slightly cyanosed. There was no history of rheumatism. Five or six years ago he met with an accident, and again, two years ago, when he fell over a "tipping" with his horse and cart. Though not materially injured at the time, he felt as if he had had a shock. From this date he became extremely nervous, and began to lose all his energy and pluck; he became afraid even of his own horse. He now began to suffer from attacks of violent palpitation, which would last for several days, and within the last three months he has been seldom free from these attacks of palpitation and a sense of cardiac distress for more than a week at a time.

When seen first by Dr. Farquharson in these attacks the pulse rate was generally from 190 to 230 in the minute. In his quiet state the pulse seldom exceeded 90, and when this was the case there could be heard a well-marked mitral systolic murmur. There was no albuminuria, no distended jugular veins, and no œdema of feet, but the left pupil was noticed to be smaller than the right—a condition of things which became more pronounced, Dr. Farquharson stated, if the stomach were distended with flatus. He had lately been the subject of dyspepsia and constipation, and when these were present his cardiac distress was increased. Beyond a sense of discomfort, of præcordial pain and uneasiness which the excited action of the heart caused, there was no marked dyspnœa. His sleep was broken and fitful. By his illness he had been rendered quite unfit for work.

The slight cyanosis alluded to was noticed in the lips, on the face, and in the finger ends. The pulse was small and extremely rapid. I counted up to 240 beats in the minute and then lost it. It was upwards of 250 on Dr. Farquharson's reckoning, but on this point we speak guardedly. Knee-jerks were slightly exaggerated. The lungs were perfectly healthy. Heart: the apex beat, which was very diffused, was felt two inches external to the nipple; there was also marked epigastric pulsation; pulsation, too, was seen and felt to the right of the sternum at the level of the right ventricle. The area of cardiac dulness was increased transversely. The tap of the heart could be seen and heard quite distinctly several inches from the chest—I thought about two feet. Over the aortic area—extending up to the episternal notch and down the sternum to the xiphoid cartilage—was heard a rough grating systolic murmur, followed by a well-marked second sound. It was only by counting the loud second sound of the heart that we were able to estimate the rate of cardiac pulsation. In addition to the grating systolic murmur mentioned above a soft mitral systolic could be heard, which was carried towards the left axilla, and particularly towards the back at the level of the fifth dorsal spine. Pressure upon the pneumogastric nerve in the neck slowed the action of the heart. The urine was normal; the internal organs of the abdomen appeared to be healthy.

We arranged that he should have 30-minim doses of tinct. belladonnæ, with small doses of Fowler's solution; that for a few days the ether spray should be applied to the back of the neck, and afterwards the interrupted current to the pneumogastric, one pole behind the neck high up, and the other along the course of the nerve in the neck. Within a fortnight he was very much better. His pulse was never higher than 120 a minute, and that only during excitement. A sphygmographic tracing taken at this time showed low arterial tension and well marked dicrotism. There was still the well-marked pericardial grating and mitral systolic murmur. The area of cardiac dulness remained as before; in its lateral diameter it measured 6½ inches.

It is now seven months since I saw him, and Dr. Farquhar-