As a preliminary to trying to determine the means that may be used to try and lessen the physical causes of mental dullness, Dr. Warner has given a table of the conditions and group of conditions accompanying it, and has determined, as far as the present work goes, the correlative value of each sign in development and nerve action observed, as well as the distribution of these signs in certain areas or districts, and in certain classes of schools and in the Nationalities. The percentage of mental dullness rises from 38 for development cases without nerve signs to 43 when both are present, reaching 44 when the maldevelopment is accompanied by low nutrition and abnormal nerve signs.

Development Cases Considered in Relation to Sex and Residence.—If we take 100 boys and 100 girls with defects in development from among the 50,000 children seen, we shall find many of them with abnormal nerve signs, low nutrition, and mental dullness. Following the experience gained, the following estimate may be given showing the probable results of placing them first in a day school and then in a resident school.

In the Day School.

Boys' Side.				Girls' Side.			
100 boys with defects in development.				100 girls with defects in development.			
Nerve cases ...	...	...	50	Nerve cases ...	...	...	47
Nutrition low ...	...	...	23	Nutrition low ...	...	...	38
Reported dull ...	...	...	38	Reported dull ...	...	...	40
Cases of nutrition low, nerve signs, or dull ...	...	...	111	Cases of nutrition low, nerve signs, or dull ...	...	...	125

In the Resident School.

Boys' Side.				Girls' Side.			
100 boys with defects in development.				100 girls with defects in development.			
Nerve cases ...	...	...	62	Nerve cases ...	...	...	52
Nutrition low ...	...	...	16	Nutrition low ...	...	...	20
Reported dull ...	...	...	40	Reported dull ...	...	...	44
Cases of nutrition low, nerve signs, or dull ...	...	...	118	Cases of nutrition low, nerve signs, or dull ...	...	...	116

It is thus obvious that residence contrasted with home life and day school produces marked effects, different among boys and girls. On both sides of the resident school nutrition becomes higher, more markedly with the girls. Nerve signs increase with residence, especially with boys. Mental dullness increases with residence slightly, more so among the girls.

The loss and gain from putting 100 boys and 100 girls with defects in development in resident schools may be represented thus:

	Boys.	Girls.
Fewer cases of low nutrition ...	7	18
More cases of abnormal nerve signs ...	12	5
More cases of mental dullness ...	2	4

Assessment of Results of Intellectual and Physical Training in a School, with Allowance for the Physical Condition of the Children.

—Having obtained a report on the physical condition of the children in a school, we may proceed to estimate the number of dull children and the number with nerve signs to be expected upon allowance for the material in the school. The estimate is founded upon the conditions seen and the average experience of 50,000 children, the allowance being made upon the development cases and nerve cases; an allowance for low nutrition could be added.

There are two results of physical training which characterise it as satisfactory: (1) in cases of defective development to remove or prevent abnormal nerve signs; (2) in children of normal development to prevent, or at least not to produce, nerve signs. Thus, taking the development cases in a school, a high percentage of abnormal nerve signs among them is against the effects of the training; and a high percentage of nerve cases without defects in development suggests that the training is not good. So also, in each case a high percentage of mental dullness shows want of adaptation of methods of teaching to the special requirements of the children.

A form is given (see Report) upon which the principal facts observed in a school may be recorded; from these estimates may be made. We may estimate as dull children:—

	Boys.	Girls.
per cent.	per cent.	per cent.
Of development cases with nerve signs ...	43	43
Of development cases without nerve signs ...	33	39
Of nerve cases without development defects ...	37	41

We may estimate as the average number of cases with nerve signs:—

	Boys.	Girls.
per cent.	per cent.	per cent.
Of the development cases ...	55	49
Of the total number of children seen as presenting nerve signs without defects in development ...	5	4

The work that has already been done, and the report from which extracts are given, afford a considerable amount of evidence to the following propositions:—

A. It is practicable to inspect, report upon, and classify the children seen in a school by means of facts seen and the teacher's report. Evidence of scientific value is thus obtainable of importance to the State, to education, and to philanthropic efforts.

B. The average child material in a school or district may be determined. The conditions of development and the nerve signs vary much in different schools; as to the latter, observation suggests that adapted methods of training may remove them.

C. The correlation of visible signs with low nutrition and mental dullness has in many cases been demonstrated.

D. Ill-made and feeble children tend to gravitate to the Poor-law and certified industrial schools, and to the lower standards of day schools. The want of provision for feeble children in day schools, and in many cases their exemption on medical certificates, tends to throw such cases upon the care of the State, and many become degraded.

E. Feebly-gifted children, the paralysed, and in some cases the epileptic, may in many cases and in limited numbers be educated in day schools if better provision for them is not provided.

REMARKS MADE AT THE

DISCUSSION

ON

PHAGOCYTOSIS AND IMMUNITY,

At the Pathological Society of London, March 15th, 1892,

BY

M. ARMAND RUFFER, M.D.Oxon.

WHEN beginning their remarks on immunity and phagocytosis Professor Burdon Sanderson and Dr. E. Klein stated that they could not accept Professor Metschnikoff's views. I will imitate their candour, and define my position in the same manner, by stating at once that I accept Metschnikoff's theory in its entirety.

Not one of the speakers has explained what he means by immunity; and surely this is the first point to decide. Immunity from a given disease means freedom and exemption from that disease. As far as I am aware, there is no animal, whether naturally resistant or protected by artificial means, which cannot be killed by the introduction of a specific microbe, provided a sufficiently large dose be used. To talk of an animal being immune against a given microbe is to speak of something which does not exist, and, although I must confess to having used the word myself, I would in future rather talk of animals naturally resistant and artificially protected.

Now when a naturally-resistant or artificially-protected animal is inoculated with a virus, I believe that the destruction of the micro-organisms in that animal is accomplished by the amoeboid cells, which, for the sake of convenience, we will call phagocytes. I am not aware that Metschnikoff, or any of his pupils, ever said that this was the only cause of the increased resistance of such animals. Metschnikoff certainly never said so, but in his writings and in conversation he has simply stated—and indeed proved—that the process of phagocytosis was one of the most important factors in the acquired or natural resistance of a given animal against a given micro-organism.

Dr. Woodhead has already stated what we know of the origin of phagocytes, and I would not enter into the discussion of this question were it not that I must make a personal explanation. I have not said anywhere that all microphages, epithelioid cells, etc., were derived from leucocytes; what I have said is that in the cases I have observed the macrophages

were derived from small lymphocytes. Were any proof necessary that such an origin of plasma or epithelioid cells is of no infrequent occurrence, I would point out that the development of these cells can be seen in the intestines of various animals, where they wander into the epithelium layer; that they have been found in the blood vessels; that when vermilion is injected into the veins of an animal, similar large cells seize on the powder circulating in the blood and carry it into the neighbouring tissues—into the medulla of the spleen or alveoli of the lungs, for instance; that no such cells are present in the alveoli of the lungs of a newly-born guinea-pig until they have been attracted there by some kind of noxa; and, lastly, that in invertebrata the transformation of an amoeboid cell into a fixed cell has actually been followed day by day in the living animal.

Let us, however, pass at once to what happens when wandering cells have taken bacilli into their interior; for there can be no doubt that leucocytes have that power, and that the organisms contained in cells undergo some kind of destruction. That is a matter of observation which everyone can notice for himself who possesses a good lens, a drop of frog's lymph, and a few anthrax bacilli.

In the first place, see what happens when a protected or non-protected animal recovers from an infectious disease, or even when it dies after having resisted the malady for a considerable time. In all cases which have been studied up to the present, phagocytosis is a well-marked phenomenon. Slight, or even absent, when the animal has no powers of resistance against a given microbe, it increases with a more resistant animal, or when an animal has been artificially protected, and reaches its maximum when the disease is essentially chronic, as in leprosy and tuberculosis. Lately I have been studying human pneumonia from this point of view, and I can safely say that the human lung in this disease exhibits, in their exquisite forms, all the phenomena of phagocytosis.

Dr. Klein, in his able criticism of Metschnikoff's theories, lays special stress on the fact that, in several instances, the process is reversed, and that the leucocytes are destroyed by the bacteria, and not the bacteria by the leucocytes. This he considers a fatal objection to Metschnikoff's theory. As far as I am concerned, I may state that, in almost every one of my papers, I specially mentioned that a large number of amoeboid cells perished in the fight. I have shown this to take place in the healthy rabbit's Peyer's patch, in the diphtheritic membrane, in actinomycosis, in tubercle, in *charbon symptomatique*, etc.

I will meet Dr. Klein on his own ground, and take as examples two of the very diseases which he himself has mentioned as proving the fallacy of Metschnikoff's theory—namely, leprosy and tubercle. In many particulars these two diseases resemble each other strongly, for both are caused by a hard resistant micro-organism, and, pathologically, both are characterised by the fact that the micro-organisms, whenever present, set up intense inflammation.

Let us make a section through a leprosy nodule, and stain it in the usual manner with logwood and carbol-fuchsin. I need not enter into the description of the epithelioid and giant cells always to be met with in leprosy, but at once examine the processes taking place in these cells. In some cases such cells, when crammed with bacilli, undoubtedly die, and this death is indicated by the degeneration of their nuclei, the vacuolisation of the protoplasm, and the apparent proliferation of the characteristic bacilli in the cells. That is one side of the picture, but let us look at the other side. In some of these cells the bacilli lose their definite outline and fuse together into a hard, solid, resistant mass, in which no structure is discernible even when use is made of the most delicate staining reagents and the highest powers at our command. In a later stage this hard resistant mass gradually breaks up and loses its power of retaining staining matter, until nothing is left in the cell but a clear space, which may be either a vacuole, or possibly a kind of membrane with which the bacilli have surrounded themselves. On one hand, therefore, we can follow the victory of the bacilli over the cells, and, on the other, we have that of the cells over the bacilli. True, in the large majority of cases of leprosy, the bacilli gain the victory, but are we not justified in thinking that the chronic character of the disease, which may last for

months and years, is due to the way in which amoeboid cells incorporate the bacilli and destroy a large number of them? Unfortunately, the bacillus has means of defence of its own, and thus frustrates the beneficent endeavours of the cells.

It is an admitted fact that in cases of tuberculosis bacilli are often found in epithelioid and giant cells, and there is not the slightest doubt that these cells frequently succumb in the fight. Signs of degeneration are found in microphages, mononucleated, epithelioid, and giant cells, with a frequency which can leave no room for doubt. But what is not so easily observed is the other side of the fight, in which the bacilli perish. Metschnikoff has shown that signs of the encapsulation, decay, and death of the bacilli are of the most frequent occurrence in the giant cells of tubercle, and more especially in the giant cells of those animals which exhibit a strong resistance towards the bacillus of tubercle. In man, indeed, such forms of encapsulation are met with in the more chronic forms of tubercle, such as old scrofulous glands or calcified nodules in the lungs. In many cases of tubercle, therefore, the bacilli prove too strong for the amoeboid cells, but that in many others the cells are victorious is proved by the frequency with which cured tuberculous lesions are found at the *post-mortem* examination of patients dying from some other disease. As Dr. Klein has said, in these diseases a great many of the leucocytes perish, but he might have added that the destruction of the bacilli is even more marked than that of the cells.

I am willing to allow the accuracy of Dr. Klein's experiment, when, on injecting a quarter or half a syringe of fluid containing anthrax spores or anthrax bacilli, he finds the anthrax bacilli in the blood a few minutes afterwards. Indeed it would be wonderful were it not so, for the frog's phagocytes are able to arrest a certain number of bacilli, but not an immoderate number; they will arrest enough bacilli to kill a mouse, but not the number of micro-organisms which would kill an elephant. And similarly with vermilion. In my experiments I injected one drop of a saline solution holding vermilion in suspension, and found that it was absorbed through the agency of leucocytes. Had I injected a quarter or half a cubic centimetre, the vermilion might possibly have penetrated directly into the blood; but I hold that it is not a satisfactory experiment to inject into the lymph cavity of a frog a large quantity of fluid, when the object in view is to study the absorption of solid particles.

In a former paper I have shown that in animals exhibiting some resistance against the bacillus of Chauveau, the disease was strictly limited to the point of inoculation and its immediate neighbourhood. When, however, from any cause, physical or chemical, the amoeboid cells were prevented from approaching the virus, the disease became general and the animal died. Dr. J. H. Walker and myself have recently obtained one more confirmation of this law, as shown by the following experiments¹ with another micro-organism.

If an adult guinea-pig be inoculated subcutaneously with 0.25 cubic centimetre of a pure culture of the bacillus pyocyanus, an abscess slowly forms at the point of inoculation. Twenty-four hours after the injection the point of inoculation is crowded with bacilli and well-filled phagocytes; but—and this is the important point—cultures made with the various internal organs prove absolutely sterile. The bacilli, therefore, are arrested at the point of inoculation by the amoeboid cells, and this can be proved by microscopic examination.

Now if at the same time that we inoculate the bacillus pyocyanus on one side of the body, we inject on the other side a large dose of chloral hydrate, which is yet not sufficient to cause death, and repeat the dose from time to time, so as to keep the animal fully anaesthetised, it invariably dies within forty-eight hours, and all the organs contain the bacilli in incredible numbers.

It is easy to prove that in an anaesthetised animal the leucocytes are inactive. Let us take two small sponges, fill them with a pure culture of the bacillus pyocyanus, and place each under a guinea-pig's skin. One of these animals we leave as a control, whereas we inject the usual quantity of chloral hydrate under the skin of the other. Six hours afterwards, when we take out both sponges, we find the fluid in the sponge of the chloralised animal almost as clear as when it was introduced. A few leucocytes may be seen in

¹ These experiments will be related in full at some future date.

it, ten or twenty at most in one cover-glass preparation, whilst the control sponge is filled with a thick purulent material, which, on microscopic examination proves to consist of innumerable well-laden phagocytes. No wonder, then, that when the leucocytes refuse their work the bacilli should find their way into the tissues. We have vainly sought for any evidence to show that the fluids of chloralised guinea-pigs are better cultivating media for the bacillus pyocyaneus than those of a non-chloralised animal; in both chloralised and non-chloralised animals the bacilli seemed to thrive exceedingly well in the fluids of the living body. Here, then, we have another instance of the part taken by phagocytes in the limitation of the disease.

As to the substances which attract the amoeboid cells towards the virus, they have been proved to be the poisons secreted by micro-organisms, or contained in their bodies. It is probable also that in some cases these poisons have the opposite effect, namely, that of repelling amoeboid cells. I have lately gained considerable evidence to show that the same substance may attract or repel leucocytes according to its state of concentration. I may mention one such experiment. If a small piece of sterilised sponge be soaked in pure turpentine and placed under a guinea-pig's skin, it will be found that, even after a lapse of twelve hours, not a single amoeboid cell has penetrated into the sponge. Sections made through the sponge and surrounding parts show that the amoeboid cells have emigrated in considerable numbers into the tissues around, but that they are arrested at a certain distance from the sponge, and can proceed no further. A piece of normal sponge placed a little distance off is absolutely crammed with amoeboid cells, though the turpentine sponge contains none at all.

Now allow a similar sponge to soak in a very dilute solution of turpentine in olive oil, and place this sponge, together with another containing fine sterilised olive oil and a third soaked in pure turpentine, under the skin of a guinea-pig. After four hours the sponge in the solution of turpentine in olive oil is crammed with amoeboid cells, whilst the other sponge soaked in olive oil contains but a few, and that in turpentine none at all. Here, then, we have the same substance exhibiting totally different effects according to the concentration with which it is applied. It is very probable that such is the case with bacterial poisons also, and there are already some experiments which support this view. Moreover, as Dr. Woodhead has already pointed out, the same substances which in a non-resistant animal repel amoeboid cells, attract these same cells in considerable numbers when the animal has been artificially protected.

When once the poisons secreted by a particular kind of micro-organism have penetrated into the system, it would appear as if in many cases the leucocytes had lost the power of leaving the blood vessels in order to attack the invading micro-organisms. This loss of power is clearly not always due to a paralysis of the cells, as these still emigrate freely in order to attack certain other bacilli, but results from some other cause still shrouded in mystery.

I must refer to Dr. Klein's theory that the cells in the lymphoid tissues attract micro-organisms, and that "the bacteria find in the cells some attractive chemical substance which suits them, and hence these cells, far from being the enemies of the bacteria, are, on the contrary, their places of refuge for a time at any rate. This view seems to me just as feasible as Dr. Ruffer's views that because these cells contain bacteria therefore they are the chief and only bacteria-destroyers." Dr. Klein supports his views by two series of facts, namely, 1, that in a great many diseases the cells are destroyed by the bacteria, an objection which I have already answered; and, 2, that in a great many bacterial diseases the bacteria are found in the lymphoid tissues of certain organs.

In my lecture, previously referred to, I alluded to the fact that when the micro-organisms are inoculated into an animal, the amoeboid cells are attracted to the point of inoculation, and that by Dr. Klein's theory it was difficult to account for this phenomenon. In his reply he states that I misunderstood him, and that he referred to what takes place in the internal organs. I am sorry that I made this mistake, but nevertheless my argument loses none of its force; for clearly the phenomena at the point of inoculation must be first

taken into consideration, and an explanation given which will reconcile Dr. Klein's theory with the phenomena observed. With regard to what takes place in the internal organs, the only evidence in favour of this theory is that micro-organisms are often found in cells. But I contend that this is not sufficient. Should anyone meet a dead lion and find a lamb inside, he, knowing the habits of the lion, would not conclude that the lamb had taken refuge in that. True, after a surfeit of lamb, the lion might die of indigestion, but the chances of the lamb ever getting out alive would be very small. Similarly, knowing the voracious habits of the lymphoid cells of internal organs, before we can accept this theory, observations must be made showing that the bacilli of their own accord force their way into the cells; explanations must also be found for the fact that the micro-organisms perish in the cells in enormous numbers; and lastly he must explain why, according to Bardach, Sudakewitch, and others, animals normally resistant against a given microbe succumb almost invariably when the spleen is removed.

Remember also that phagocytes exert a distinct choice between two kinds of microbes. They will leave the bacillus of tetanus for the micro-bacillus prodigiosus, and the streptococcus for the bacillus of diphtheria. This is well illustrated in the diphtheritic membrane, where at the surface one can see leucocytes taking in numbers of bacilli, but leaving streptococci almost untouched; with the immediate result that streptococci are often met in the deeper parts of the membrane, and with the remote result that secondary abscesses occurring in the course of diphtheria are never due to the bacillus of diphtheria, but to some other micro-organism.

The study of the diphtheritic membrane shows the remarkable resisting powers of leucocytes, for although the tissues underlying the membrane are necrosed and dead, the leucocytes have the power of marching in their numbers right up to the bacilli and waging war against them, though many, as I have shown, perish in the fight.

Some investigators, the chief of whom is Dr. Buchner, of Munich, have laid great stress on the bactericidal action of the serum of resistant animals. I may perhaps be permitted to express my great admiration for Dr. Buchner's work and that of his followers, and I am ready to allow that the facts, as stated by Dr. Buchner, are in the main correct; but I am far from accepting the view that the fluids of the living animal play any part in the destruction of microbes in the organism.

In the first place, let us see what happens in animals which have undergone no protective treatment. If the bactericidal action of normal serum has anything whatever to do with the resistance of animals towards a particular kind of microbe, then whenever the resistance of an animal against a given microbe is great, the bactericidal action of its serum on that microbe should also be marked; and that when an animal is not resistant, the bactericidal action of its serum should be feeble, or at least slighter than that of a more resistant animal. A rabbit is not resistant, and its serum possesses a strong bactericidal action on the anthrax bacillus; a dog is more resistant, and its serum has no bactericidal action on the anthrax bacillus. We have one exception, that is the white rat, which possesses considerable resistance against anthrax, and the serum of which has a strong bactericidal action on the bacillus anthracis *in vitro*. But this exception proves the rule, for when the bacillus anthracis is inoculated into a white rat, it thrives at first remarkably well, though it is ultimately destroyed by the animal's amoeboid cells. That teaches us another thing also, namely, that it is impossible to argue that those phenomena which occur *in vitro* exclusively take place in the living body.

Were other examples necessary, I would draw attention to the fact that, *in vitro*, the serum of the non-resistant rabbit is a bad cultivating medium for the bacillus pyocyaneus, whereas the serum of the resistant guinea-pig is an excellent cultivating medium for the same bacillus. And conversely, I would point out that the serum of the resistant rabbit is an excellent cultivating medium for the bacillus of Chauveau, and that of the non-resistant guinea-pig a very bad medium for the same micro-organism. Moreover, I have proved that the fluids of both kinds of animals when alive form an excellent cultivating medium for this same bacillus. And yet another example of

a similar nature. The bacillus of diphtheria in most animals is only found at the seat of inoculation, and in rabbits and guinea-pigs never spreads any further; and yet the serum of such animals is an excellent cultivating medium for the bacillus of diphtheria.

With regard to Sanarelli's experiments with the cell-free lymph obtained from the frog's lymphatic sac, I must acknowledge that such experiments are extremely interesting, and throw great credit on the scientist's ingenuity; but I contend that, from the point of view which interests us, they prove absolutely nothing.

This gentleman placed particles of organs of an animal dead of anthrax in a small closed collodion bag, from 3 to 4 centimetres in length, and capable of holding about 1 cubic centimetre, and inserted the whole in the lymph sac of a frog. Three or four days afterwards he removed this bag, and placed it under the skin of another frog; and then, after a like period, under the skin of a third frog. Examining its contents on the eighth or tenth day after its introduction into the lymph sac of the first animal, he found that no leucocytes had penetrated into the bag, but that the anthrax bacilli were mostly degenerated, and no longer capable of reproducing the disease when inoculated into a non-resistant animal. Now, it is almost impossible to introduce a bag measuring more than one inch under the skin of a small animal like a frog without producing not only serious lesions, but without grave risks of contamination also. In Sanarelli's paper there is nothing to show that the fluid bathing the outside of this bag was aseptic. Moreover, when we remember how leucocytes will force their way in a few days into such hard, resistant objects as bone and ivory, it is difficult to believe that the inside of these thin collodion bags should have been free of leucocytes. But granting the fluid outside the bag was completely aseptic, and that no leucocytes had penetrated into the bag, I do not allow for one moment that the lymph contained therein was normal, such as that found in living animals.

The lymph during the last days of the experiment was a mixture of three different kinds of lymph, collected during eight or ten days from three different frogs. Were any evidence necessary to show that this lymph was quite abnormal, I would point to Sanarelli's own paper, in which he says that the histological elements of the tissue introduced into the bag were so altered that they were perfectly unrecognisable. Would anyone maintain that normal lymph will destroy such a hard resisting element as the nucleus of a cell?

Interesting, therefore, as are Sanarelli's experiments, they prove nothing as to the bactericidal action of the normal lymph of a frog.

It has been proved experimentally that after an animal has been artificially protected against a given infectious disease, the serum of such an animal *in vitro* is a bad cultivating medium for the micro-organism causing the malady, and by some this has been set down as a general rule. This is not so, however, for the serum of animals artificially protected against the bacillus of diphtheria possesses no bactericidal action on the bacillus of that disease, and the same remark holds good for tetanus. As I was writing this paper I received a copy of a paper by Mossig, in which he states that the serum of rabbits artificially protected against the pneumococcus is a far better cultivating medium for the pneumococcus than the serum of a normal animal. This bactericidal power of serum is therefore not an essential corollary of the increased resistance of artificially-protected animals. Moreover, our knowledge of it is at present extremely unsatisfactory, for there is no evidence to show whether it be a specific power of the serum on the micro-organism producing the disease, and on that micro-organism only; and we have no knowledge as to how long the serum of the animal retains this bactericidal power. I have very strong reasons for thinking that it is only of a very transitory nature, passing off long before the animal has lost its increased resistance. However that may be, see what happens when an animal is inoculated with a micro-organism on which its serum exerts its bactericidal action *in vitro*. For I repeat it, what we want to know is not what happens when a micro-organism is introduced into a test tube together with that wholly-artificial substance called serum, but the point is what happens when it is introduced into the living tissues and blood of an artificially protected animal. I may perhaps be pardoned if I again refer to a series of experiments which Dr.

J. H. Walker and I made on guinea-pigs, the resistance of which had been strengthened by a previous inoculation of the bacillus pyocyaneus. We chose this bacillus because my friends MM. Charrin and Roger have shown that the blood of animals artificially protected against this micro-organism possess strong bactericidal powers.

The guinea-pigs, which naturally possessed a high degree of resistance against this bacillus, had been further protected by an inoculation of 0.25 cubic centimetres or 0.50 cubic-centimetres of a virulent culture of bacillus pyocyaneus, and at the time we used them for our experiments they were perfectly recovered and proved to be efficiently protected against this bacillus. The skin of the animals was carefully shaved and two drops of a bouillon culture were injected under the skin. This dose does not produce the slightest symptom in protected animals. The first guinea-pig was killed by chloroform 20 minutes after the operation, and cover-glass preparations were made from the seat of the puncture and stained with Loeffler's blue. In each slide several leucocytes were found already crammed with bacilli, while a great many micro-organisms were floating in the exudation fluid, and showed not the slightest sign of degeneration. Cultures made from the point of inoculation gave an abundant crop of perfectly healthy and normal bacilli.

Another animal was killed after two hours. Here the leucocytes were already in far greater numbers and contained numerous bacilli. The micro-organisms floating free in the exudation fluid were absolutely normal, and grew abundantly on agar, gelatine, and bouillon.

Another guinea-pig was examined after six hours, and the point of inoculation was full of multinucleated amoeboid cells, every one of which was crammed with bacilli. A large number of organisms were still free, and consisted of short, straight, and extremely motile organisms which grew abundantly on various cultivating media.

The fourth guinea-pig was killed after ten hours, and presented much the same appearance as the last; whilst in one killed twenty-four hours after the inoculation the leucocytes had emigrated in incredible numbers and the number of bacilli floating freely in the exudation liquid had correspondingly decreased, although such of them as remained free were marvellously active. A culture was made from the point of inoculation, and this proved to contain nothing but the bacillus pyocyaneus.

Although the bacilli had remained for twenty-four hours in the living fluids of this doubly-resistant guinea-pig it was impossible to detect the slightest sign that the fluids of the living animal had exerted their vaunted bactericidal action. On the contrary, they proved excellent cultivating media for the organisms.

Further, we found that the cultures made with the bacillus pyocyaneus, which had lived for twenty-four hours under the skin of a guinea-pig proved excessively virulent; and in one case, of a rabbit artificially protected and inoculated straight into the veins, we found active and virulent bacilli eight days after the inoculation.

Some observers object to the use of filter paper for wrapping up the virus when the object in view is to study the bactericidal action of the fluids of living animals on the grounds that it may arrest some of the bactericidal constituents of the lymph. It is strange that these gentlemen should bring forward this argument, as they accept the evidence based on serum which has been filtered through a porcelain filter, and it has been the boast of some observers that the bactericidal action of serum could not possibly be due to the cells contained in it, as the bactericidal action was not abolished by passing through porcelain. In fact, these gentlemen strain at the gnat but willingly swallow the camel. As a matter of fact, however, I showed that leucocytes in a few hours had made their way through the filter paper into the interior of the bags, and it is clearly impossible to suppose that the same paper which is unable to arrest leucocytes should prove an effectual barrier to a chemical substance.

The increase of virulence in the tissues of artificially-protected animals is a result which might have been foretold; for, if any micro-organisms survive at all in such animals, they must be those which, from some cause or other, possess qualities enabling them to resist the attacks of leucocytes, and to adapt themselves to their new medium. A short time

after the inoculation, all the weaker micro-organisms must have been destroyed whilst only the stronger ones survived, and by this process of elimination a more hardy race of bacilli must have been obtained. And do we not see the virulence of anthrax increased by passing through resistant animals, such as dogs and pigeons, the bacillus Chauveau rendered more virulent by living in the subcutaneous tissues of resistant animals? But I will leave this point, as most probably Dr. Cartwright Wood will shortly have more to say on this subject, though I must again insist on the fact that in a large number of bacterial diseases, if not in all, there is no evidence to show that the fluids of a living resistant animal have the slightest attenuating action on the micro-organisms causing the disease.

I think there are few pathologists who will not readily confess to the feeling of intense astonishment which seized them when they first read Ogata and Jasuhara's paper, or rather the account of it as it appeared in the *Centralblatt f. Bakteriologie*. Everyone had been trying to find a remedy against anthrax, and everyone had failed; and now it was sufficient to inject the minutest drop of a resistant animal's blood under the skin of another animal to cure it of anthrax. True, there were a few points in the experiment which did not appear quite clear, but still the evidence seemed fairly conclusive. Unfortunately, when other experimenters tried to reproduce these results they failed without an exception. But, for the sake of argument, we will suppose that Messrs. Ogata and Jasuhara's results are correct, and that for some reason or other the other experimenters were wrong. Granting all this, even then I do not see how Dr. Klein's contention holds good that the cure of anthrax in these cases may be due to the antiseptic powers of the injected blood.

In the first place the quantity injected was infinitesimally small, and it was not always injected on the side where the virus was introduced, but occasionally on the opposite side; so that this drop of dog's or frog's serum, before it had the opportunity of acting, was diluted in the whole of the blood of a mouse inoculated with anthrax. Moreover, when we come to see what is the action of dog's blood on anthrax bacilli, we find that it has only a very weak, if any, bactericidal power; so that, if Dr. Klein's opinion be correct, we must suppose that dog's blood, which has normally no bactericidal power, when injected into a mouse suddenly exerts—for reasons not explained—such a strong antiseptic action that it is able to kill millions of bacilli introduced into the mouse's system, although diluted in the whole of the animal's blood.

And what I have said of these experiments applies with even greater force to experiments made with the serum of animals artificially protected against tetanus, which possesses no bactericidal action on the bacillus of tetanus.

Of Mr. Hankin's experiments with the proteid he obtained from the spleen of white rats, I cannot speak from the chemical point of view, but one thing seems to me certain, namely, that this action of this proteid cannot be due to any bactericidal powers it may possess, for it is impossible to believe that a dose of albuminoid matter which has the power of killing a limited number only of spores *in vitro*, should be able to destroy the millions of bacilli introduced into the excellent cultivating medium formed by the mouse's tissues and fluids. May I incidentally enter a protest against the crowd of new names with which Mr. Hankin has lately attempted to saddle our bacteriological vocabulary? To speak of alexines is scarcely scientific when their very existence is a matter of considerable doubt; but to talk of mycosozin or mycophylaxin when we have not the remotest idea what sozins or phylaxins are, or whether there are any such bodies, is hardly pardonable. Surely the first thing to do is not to give a hypothetical body a high-sounding name, but to isolate and study the body.

Truly the bactericidal properties of the serum of artificially protected animals are suggestive, and deserve to be studied, but I maintain that there is no causal relation between the bactericidal properties of the serum of a given animal against a given micro-organism and the acquired resistance against the same microbe.

One of the speakers has referred to the experiments of Behring, Kitasato, and others, in which the blood of an animal artificially protected against a given microbe possesses the property of destroying the poisons of that microbe, not

only *in vitro*, but also in the tissues of the living animal; and some have gone so far as to say that it was to this poison-destroying power of the serum that the increased resistance of such animals was due. Far be it from me to depreciate in any way the important results obtained by Messrs. Behring and Kitasato, but at the same time it is evident that this poison-destroying power of the blood is not a necessary accompaniment of the increased resistance of such animals. Thus fowls possess considerable resistance, not only against the bacillus of tetanus, but even against the poisons secreted by this bacillus; and yet the blood of fowls possesses no action whatever on the tetanus poisons. Let us turn now to animals artificially protected. Undoubtedly the serum of a rabbit protected against tetanus often possesses the power of destroying the tetanus poisons, but this is by no means *always* the case; and yet the rabbits, whose serum does not destroy the toxins, possess an increased resistance against the bacillus.

We must conclude, therefore, that, although in artificially-protected animals this property of the serum may be noticed, yet it may be absent even in protected animals, and is generally wanting in animals naturally resistant against tetanus; and also that the increased resistance of such animals is not primarily dependent on the poison-destroying power of the serum and tissues.

Another point which has been mentioned is that animals artificially protected against a living microbe can also to some extent resist the poisons of that microbe. Undoubtedly this is occasionally the case, but it is by no means a general rule, nor is this property of being able to resist poisons a necessary corollary of the increased resistance of animals artificially protected. Quite the reverse in fact; for in some cases artificially-protected animals have less resistance towards the poisons than non-protected animals of the same species. It is occasionally possible to render animals insusceptible to the poisons of the vibrio Metschnikovi, but usually those animals which are already resistant against the vibrio succumb to the action of poisons more easily than non-resistant animals.

Similarly with the bacillus pyocyaneus. Some observers have occasionally been able to protect animals against the poisons of the bacillus pyocyaneus, but in most cases they have failed, although the animals had gained an increased power of resistance. I found, for instance, that by injecting small doses of sterilised cultures at varying intervals the animals invariably died, whilst a few small doses markedly increased their resistance. The conclusion to be drawn, therefore, is that the power of resisting bacterial poisons is not a necessary accompaniment of immunity, but may be present or absent without apparently influencing in any way the resistance of animals.

There is only one class of cells which appear to possess the power of quickly becoming accustomed to bacterial poisons, namely, the cells which are designated under the term of phagocytes. No doubt means will be found to increase the resistance of other cells of the body to bacterial poisons, and far be it from me to say that such an increased resistance and the poison-destroying power of the blood and tissues of the body do not play a part in reinforcing the resistance of animals; but I maintain that at first this property is not a necessary accompaniment of the increased resistance of animals.

It has been proved that the injections of bacterial poisons so influence the cells of the body that, long after their introduction, marked changes take place in the various organs of the body—changes which often prove fatal to the animals. But no doubt the converse is true, and in other cases the changes are of such a nature that they are of assistance to the cells in resisting the action of micro-organisms and their poisons. That is a notion which is as old as the notion of micro-organisms as essential factors in the production of disease.

There are many other points which I would have liked to touch upon, more especially the evidence on the so-called immunity produced by the blood of so-called immune animals. I must leave this for a future occasion, but I may state at once that these experiments, should they prove correct, are capable of quite another explanation than that given by their authors. And may I remind the Society that, more than two

years ago, Dr. Charrin and I proved the presence of the poisons of the bacillus pyocyanus in the urine of artificially protected animals fourteen days after these poisons had been introduced; and also that we succeeded in rendering rabbits resistant by the injection of the blood of animals suffering from the pyocyanic disease. The explanation we gave of this phenomenon was a good deal simpler than that now offered us; but we forgot to coin half-a-dozen Græco-Latin words in connection with it, which circumstance may perhaps account for the fact that our discovery has fallen into oblivion.

In conclusion, it is my firm conviction that the only process which has been proved to be essential to the resistance of animals—whether this resistance be natural or obtained by artificial means—is the power that amoeboid cells possess of taking into their interior and destroying micro-organisms, and that there is overwhelming evidence to show that this process is proportional to the resistance of the animal. Finally, let me again repeat that neither Metschnikoff nor any of his pupils have ever said that this was the only cause of natural or artificial resistance.

REMARKS ON TRACHEAL TUGGING AND ON ITS CLINICAL VALUE.

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OWING to the circumstance that Dr. Grimsdale's able and suggestive thesis¹ was, of necessity, a strictly separate production, towards which nothing beyond a series of observations conducted by myself, and very kindly recorded by Dr. Grimsdale and by Mr. L. Moysey, and various incidental remarks made as the occasions arose, was contributed from me, it differs in some particulars from the account which I had intended giving of the investigation. I therefore desire to state as clearly as possible, and without entering into much detail, the leading points in the inquiry, and the main conclusions arrived at by me.

At the time when Mr. MacDonnell's paper² called attention to the subject, I had under treatment in St. George's Hospital a case of inveterate cough and bronchial catarrh, beginning, so I thought, with gouty bronchitis, and presenting the usual signs. Up to that time, neither by myself, nor, as far as I gather, by anyone else, had any suspicion of aneurysm been entertained. The existence of aneurysm of the arch of the aorta was at once revealed to me when I applied Dr. Oliver's test, and shortly after the treatment had been modified, the cough and the noisy *râles* abated, and dulness and tubular breathing could be recognised in the interscapular region and to a very slight extent in the right infraclavicular space also. The patient is still in bed, and presents several obvious signs of aneurysm, but no pulsation. He owes his improved health and probably his life, through Mr. MacDonnell's agency, to Dr. Oliver.

Since that date I have regarded "tracheal tugging" as an important aid to diagnosis; and hearing that its value was doubted owing to its presence in some healthy persons, I was led to inquire into the frequency of its occurrence, independently of aneurysm, in the two sexes, at different ages, and under various states of health. With this inquiry I combined observations as to the relative value of Dr. Oliver's method of eliciting the sign, and of that which I had happened to devise and to use from the first.

The Method of Examination.—The process recommended by Dr. Oliver is as follows:³ "Place the patient in the erect position, and direct him to close his mouth and elevate his chin to the fullest extent, then grasp the cricoid cartilage between the finger and thumb, and use gentle upward pressure on it, when, if dilatation or aneurysm exist, the pulsation of the aorta will be distinctly felt transmitted through the trachea to the hand. The act of examination will increase laryngeal distress, should this accompany the disease."

The annexed woodcut, slightly modified from a sketch very kindly taken for me by Dr. Grimsdale some months ago, illustrates the alternative method. The observer stands behind the seated patient, whose head is slightly thrown back and steadied against the observer's chest. The tips of both index fingers are then inserted under the lower edge of the cricoid cartilage, which is gently raised by them. I have

Fig. 1.—The observer is supposed to be standing behind the patient.

carefully recorded the patients' estimates of the relative discomfort of the two methods. Those with soft and tender larynx (chiefly women and children) were about evenly divided in favour of one and in favour of the other. Many others, including even some children, were quite free from discomfort under examination; and this was almost invariably the case in subjects of mature age, with stiffened cartilages. The second method has one disadvantage affecting the observer—that it is almost too delicate, the fingers appreciating the slightest traction, whilst accuracy of observation is favoured by the patient's head being firmly steadied.

The Occurrence of Tracheal Tugging in the Absence of Disease of the Aorta.—Sixty male subjects and fifty-seven females were examined with both methods. In 28 per cent. of the females and in 50 per cent. of the males, some degree of "tracheal tugging" was recognised, the higher percentage in the males being partly accounted for by three cases of aneurysm which gave the tug being included in the list. This unexpected frequency appeared to detract from the diagnostic value of the sign; but, in reality, a large majority of the cases were described as "doubtful or very slight," a few as "moderate," and three only as "marked," and these were the three cases of aneurysm.⁴ In none of the females was the tugging pronounced, and in several it was present only during excitement.

Although, in a modified sense, Dr. Oliver's views had been confirmed, yet the upshot of the inquiry was to show that the significance of the sign was not so simple a question as had been stated originally, and that, before any final conclusions could be drawn, much more numerous observations were needed than I had had leisure to make. It had also come to light that some account must be taken of the personal factor in the perception of the slighter degrees of tugging, and in the appreciation of their value.

Circumstances Influencing the Occurrence or the Degree of Tugging.—Early in the inquiry I had suspected that thoracic conformation and the size of the lungs might have some connection with the existence of this peculiarity, and I had imagined that a short thorax and pulmonary emphysema might favour the occurrence of tugging. These were only suggestions, which I have not had an opportunity of putting to the test. Two points were very clearly made out—(1) the favouring influence of cardiac excitement (this was most obvious in several females), and (2) the favouring influence of forcible inspiration. The former might have been expected. The latter is, I believe, explained by the stretching of the air passages as a whole during inspiration, and particularly by

¹ *Practitioner*, February, 1892.

² *Lancet*, 1891.

³ *Lancet*, September 21st, 1872.

⁴ In a fourth case (of emphysema), tugging was decided during expiration, but very slight during inspiration.