The "point of the jaw hit" is a horrid head-jerking affair, compared with which a flush hit on the nose, with all its concomitant stars and stripes, is a mere fleabite. Even a moderate infliction of this terrible hit is sufficiently punishing to make one feel uncertain whether you are twisting round the surroundings, or the surroundings are twisting round you, or whether both are not waltzing away together; but a severe visitation, if it does not break the jaw, is likely to produce an absence of interest in subsequent proceedings, or a complete forgetfulness of all immediate and pressing engagements.

This blow is practically never fatal, an after examination of the man shows the heart's action to be excited only in due ratio to the condition of the exertion, pulse regular and of good quality, respiration the same; there is neither contraction nor dilatation of the pupils, no squinting, no severe headache, no clammy sweat, no cold extremities, and no ashy colour of the face; in fact, none of the usual signs associated with ordinary shock or concussion.

The following degrees of severity may be noted according to the force and accuracy of the blow: (1) Giddiness and visual disturbance, with loss of equilibrium; the man falls to the ground, is able to recover almost instantly, and resume hostilities little the worse. (2) Unconsciousness, several seconds elapsing before he is able to rise; then he is shaky, uncertain in his movements; he has no recollection of the blow, and evinces surprise and indefiniteness about his position. (3) Complete loss of consciousness, prolonged for several minutes or hours, which is not followed by perfect recovery, the man being left dull and apathetic, never to gain his old nerve and courage.

Equilibrium and the semicircular canals of the ears. That these canals have to do with the maintenance of equilibrium is now an accepted fact, proved by the experiments of Lee upon dog fish, and the researches of many others in the realms of physiology and also pathology. These canals are so placed in their respective planes as to be specially adapted for this purpose. The statical explanation of their action is not proved; but the kinetic theory is to be accepted. They also have had ascribed to them the power of preserving proper muscular tone. A close relationship exists between these canals and the eyes.

The frequent occurrence of nystagmus in disease of these organs must be noted, and also the normal bilateral deviation which occurs when the head is turned in any direction.

When a moderate rotation is imparted to the body, the endolymph currents convey a stimulus to the hair cells in the canals and the ampullae (*crista acoustica*), which raises a definite and clear impression in the brain and consciousness, and we are aware of movement and change of position, independent of vision altogether, though more accurately determined when the eyes are called into play.

A slight exaggeration of this occurs when a moderate blow is received on the point of the jaw; the head is jerked suddenly round on its axis, and this rotatory movement sets up currents in the endolymph, which, if the force be applied in the horizontal plane, cause surrounding objects to appear to move around; but if the plane be altered towards the vertical in more or less degree these objects seem to dance up and down as well.

But let the blow be severe and then the rotatory movement is so intense that the nerve endings are stunned by the force of the sudden impact of the endolymph, the power of sustaining equilibrium is lost hopelessly, and the man falls to the ground in an unconscious condition. As soon as the fluid gains a condition of quiescence, he is able to grasp the situation, opens his eyes gradually, aided by touch and sight he regains his feet and soon feels himself again.

Captain Edgeworth Johnstone² states that the sudden twisting of the head, which he also recognizes as the primary movement, causes probably a jarring of the medulla oblongata, and a temporary constriction of the vertebral arteries, and anaemia of the brain; but this view I cannot accept.

We cannot constrict these vessels by merely normal rotation of the head, if they were constricted the symptoms produced would be entirely different from those I have described; we should experience them if our heads were twisted round beyond a certain point, which is not so; and again all these effects (concussion which in the severest type is added being eliminated) may be experienced if the body as a whole be rotated on a moving platform.

A centrifugal drying machine was, on one occasion, accidentally set in motion while a friend of mine was in it, and though quickly stopped, the inmate was already blind, helpless, unable to stand, and his memory was seriously affected; but all the symptoms speedily disappeared after a rest on the back.

A careful consideration of the signs I have endeavoured to describe will at once show that there is present something more definite than concussion and shock. The rotation of objects seen by the eyes in different planes is in direct relation to the direction in which the force of the blow falls, the several degrees of intensity in ratio to the amount of force of impact, and the speedy recovery in all but the most severe cases, when probably other elements come into play; and the fact that the blow must be such as to impart a rotatory movement to the head, or head and body as well; a flush hit straight on the nose, between the eyes on the side of the head, will knock a man down; but not with the signs of equilibrial disturbance; all point, in my opinion, to their origin in the endolymph in the semicircular canals.

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- ¹ *Boxing*, Sports Library, by Allanson-Winn, p. 55. ² *Boxing*, by Captain Edgeworth Johnstone, p. 147.

The Goulstonian Lectures

ON

THEORIES OF IMMUNITY AND THEIR CLINICAL APPLICATION.

Delivered at the Royal College of Physicians, London.

By A. S. GRUNBAUM, M.D. CANTAB., F.R.C.P.,

Director of the Cancer Research in University College and the Royal Infirmary, Liverpool: Assistant Physician, Liverpool Hospital for Consumption and Diseases of the Chest.

LECTURE III.

ACTIONS OF CURATIVE SERUMS OTHER THAN ANTITOXIC AND BACTERICIDAL.

WE have seen that the introduction of the serum of one animal into the tissues of another, especially of a different species, leads to the formation of antidotes to that particular kind of serum. In some instances indeed the serum of one animal may be toxic for another. The introduction, therefore, of a quantity of horse serum into the human body may not be—indeed, is not—always a matter of indifference. We know that in the case of diphtheria antitoxin a certain percentage of cases have eruptions, joint pains, etc., which are probably to be assigned to the alien serum. Perhaps the juvenile serum is of a more primitive nature than the adult, since children are said to stand prophylactic injections of diphtheria antitoxin better than those already grown up.

But in the case of antitoxic serums these side-chains do not interfere with their efficiency. Nor will any harm arise from a dose beyond what is necessary for mere neutralization of the toxin: on the contrary, the excess may dissociate a union of toxin and cell already completed. There is not at present any evidence to show that the toxin formed by the *B. diphtheriae* in the human body is not efficiently neutralized by the antitoxin formed in the horse's tissues.

With bactericidal serums the case is rather different, because for their efficient action both amboceptors and complement are required. It is obvious that efficiency will be attained only if both components are present in sufficient quantity, but it is the number of amboceptors resulting from the process of immunization which will determine to a large extent the potency of the bactericidal serum, since they are present in normal blood only in small quantity.

The complement, as we know, is much more unstable, and may, on keeping of the bactericidal serum, either disappear or be converted into complementoid. On the other hand, complement is present in quantity and variety in normal serum, so that the introduction of amboceptors alone in the bactericidal serum will often suffice for its efficient action. But the quantitative relations of amboceptor and complement are of extreme importance. It has been known for some time that a medium dose of a bactericidal serum may save an animal from a lethal infection, whilst a larger or smaller quantity fails to do so. The explanation seems to be as follows: If the two components are present in corresponding quantities the amboceptor will unite with the bacterium by its haptophore group, the complement will then fit into the complementophile group of the amboceptor, and the bacterium will be destroyed.

But with an excess of amboceptors an alteration of equilibrium takes place, and the affinity of the complementophile group of the engaged amboceptor for the complement may be altered. If increased there is no harm done, because the complements will unite with the already engaged—that is, effective—amboceptors. If the affinity remains equal the complements will be equally distributed and only half will take part in the bactericidal action, and the efficiency of the serum will be correspondingly reduced. If the affinity is diminished the result will be even more unfavourable, for then the complements will become first

attached to all the unengaged amboceptors, and only the remainder available for effective bactericidal action.

Consequently, under certain circumstances too much bactericidal serum may do more harm than good.

Even if sufficient complement be introduced with the bactericidal serum, it may lead to the formation of anticomplement, and so, although a suitable complement as such will usually be present in the immune serum used for curative purposes, it may become engaged with the anticomplement and so be rendered useless.

On the other hand, in active immunization, although so far as we know there is no increased production of complement, that already existing in the organism will fit and activate the amboceptors formed during the immunizing process.

Since the complement contents and quality of the blood can be tested against a bactericidal serum *in vitro*, it is possible to ascertain in advance whether any bactericidal serum is likely to be of use or not for any individual case. It may even be possible to artificially induce the formation of deficient amboceptors in individuals in whom we recognize a diathetic deficiency—for example, in persons disposed to tubercle—and so make good the adage of prevention being better than cure.

What are the practical applications to be learnt from these experimental investigations regarding toxins and antitoxins? In the first place, it is obvious that any antitoxic serum which we possess should be applied as soon as possible after the recognition of the illness. Since most of the evidence goes to show that the mere injection of an antitoxic serum does not appreciably stimulate the formation of antitoxins in the body; since, moreover, any definite quantity of antitoxin will neutralize only a definite quantity of toxin, the object should be to inject before much toxin is formed.

We know that the toxins act directly on certain cells, and may have a greater avidity for them than for the corresponding receptors of the antitoxin. It may even be impossible to break the bond of toxin with cell, or possible only with a large excess of antitoxin: again another reason for its early administration.

The experimental investigations regarding tetanus and its antitoxin also give a clue as to the mode of application of antitoxin. In this instance we know that the toxin especially attacks the nerve cells of the brain, and more especially, it would appear, those of the motor area. Consequently it appears advisable to apply the antitoxin somewhere in proximity—namely, subdurally or intracerebrally, so that it may fix the toxin before it is bound or before it is indissociably bound or has destroyed the nerve cell. There is, to my mind, much more hope for cure in man in the particular case of tetanus, because the toxin is formed but slowly at the site of inoculation, and not introduced comparatively rapidly into the circulation as in experiments with animals.

Very little antidote is formed in certain cases in man, even when the attack is mild or successfully resisted, for example, in septicaemia. For this reason the administration of the serum should be continued for some time after apparent recovery until its action is quite complete. Since the antidotes are often not destroyed by digestion, it should be remembered that a curative serum may often be given with good result by the mouth.

Remembering also the ease with which the complement becomes inactive, it is obvious that all curative serums should be used as fresh as possible. Antivenomous serum undergoes a comparatively rapid and great deterioration in the climate of India.

INCUBATION.

By the incubation period of a disease we usually understand the period elapsing between the exposure to infection and the appearance of symptoms. We know that in different individuals this period will vary. The theory of immunity offers a rational explanation. We shall see how individuals differ both as regards the mediators and also the complements present in the blood. It is only to be anticipated that this variation, representing as it does a variable power of resistance to the bacterial invasion, will cause differences in the time taken until such reserve shall have been used up, that is, until infection is in full swing. Moreover, since the infective agents may also vary both in strength and in number, an additional factor for marginal differences is introduced. But the incubation period includes a number of processes and phenomena which are not expressed or explained in such a diagrammatic description. With the more slowly-acting poisons the incubation period cannot be reduced below certain limits, however great the dose administered.

According to Ehrlich's theory—but this explanation is not admitted by his opponents—the incubation period results from the separate action of the two groups in the toxin; the haptophore group becomes gradually attached, and not until this process is complete can the toxophore group act. The following experiments support this supposition: Frogs injected

with tetanotoxin and kept at 8° C. do not develop tetanus; but they do if subsequently exposed to a temperature of 38° C. They can be saved by the injection of antitoxin before being raised to 38° C., but the longer the interval between the two injections the larger the dose of antitoxin necessary. On the other hand, if a "warm frog" be injected with tetanus toxin, and after twenty-four hours, but before there are any symptoms of tetanus, be cooled, no symptoms develop. But if now antitoxin be injected and the frog again made warm, tetanus nevertheless develops, and cannot be arrested by any dose, however large, of antitoxin. The union of toxin to nerve cell occurs so rapidly and completely in the warm frog that subsequent disruption by antitoxin is no longer possible.

There is experimental proof to show that such a union can be undone and it can be explained only on the supposition of mass action and greater avidity of the antitoxin.

It has been objected by some that no proof is afforded by these experiments of a separate toxophore group in the toxin molecule. This objection is valid, but there is also nothing in these observations inconsistent with such a supposition, far less anything to disprove it.

EFFECTS OF PROTECTIVE INOCULATION AND INFECTION ON IMMUNITY.

It might have been supposed that an attack of a disease would be the most effectual way of conferring immunity. Within limits this supposition is probably correct. In small-pox we know it to be so, and if the *causa morbi* be at all analogous in scarlet fever, measles, etc., it is very likely to be the same with these diseases.

But in those infections of which we know the micro-organism it happens that the individual may survive an infection and yet have no antitoxin in his blood. Both men and guinea-pigs recovering from tetanus have generally no antitoxin in their circulation. The attack on the cells is so severe that only a sufficient quantity of side-chains is formed and no excess. A mild attack will confer more immunity than a severe one.

Consequently for protection against such diseases a process of slow immunization is preferable. In the case of typhoid it would appear that various strains of the bacillus should be used; and since the immunity conferred does not last long, revaccination at comparatively short intervals is advisable.

This procedure is far more effective than any attempt to confer passive immunity by the injection of an immune serum, for it has been shown that the bactericidal antidotes are different and special for different animals.

Thus rabbits injected with goats' cholera immune serum form anti-antidotes for goats only, not for other animals. This affords further proof that the immune serum merely contains an excess of normal mediators and not new ones; also that amboceptors for any bacterial species exist separately.

The introduction of the hetero-immune serum thus leading to the formation of anti-antidotes explains the short duration of passive immunity, for the amboceptors are thus neutralized and rendered useless. On the other hand, the long duration of active immunity is accounted for by the stimulated production of mediators already naturally present, to which, of course, no antidote will be formed.

The fact that several tissues may take part in the process must be always kept in mind. Viewed in this way, the treatment of tuberculosis by injections of tuberculin is perfectly logical. One naturally feels inclined to argue that since the toxin is already being formed in the consumptive the introduction of more is likely to do harm rather than good. But it is formed at and largely limited to an area of cells obviously too weak to resist, whereas the other tissues may, and do, produce suitable antidotes. In my own opinion and experience the tuberculin cure has been unfairly discredited, and would form the most valuable part of sanatorium treatment. The latter by itself can at most induce a general resistance, possibly by securing the occupation of the nutrient receptors by nutrient molecules only. It cannot produce any specific improvement (as the subsequent tendency to relapse shows) of the diathetic deficiency in special mediators antagonistic to infection by the tubercle bacillus. This is effected by tuberculin.

RELAPSES AND REINFECTIONS.

Several reasons may be assigned in explanation of relapse. To begin with, the organism may have been so exhausted by the disease that no new adequate reproduction of amboceptors takes place. The tissue cells no longer respond to the stimulus, and the toxin or bacterium can attack the specific, most sensitive cell. Thus a horse highly immunized in the sense of having much antitoxin in its blood may yet succumb to a fresh injection of toxin by the exhaustion of its tissue cells, which now permit the toxin to proceed direct to and to poison the nerve cells. For in an actively immunized animal the toxin has greater affinity to the body cells than to the

antitoxin, whilst the reverse is the case with passively immunized animals.

On the other hand, a total loss of receptors should also lead theoretically to immunity, and experimental corroboration of this hypothesis is forthcoming in the fact that such immunized horses may stand large doses of toxin, but yield no antitoxin. In the absence of receptors there is no toxic action, and no necessity for the formation of antitoxin. The receptors for other toxins are not lost at the same time; such an animal can be and is used for the preparation of another antitoxin.

But relapses may also be explained in another way. The evidence regarding agglutinins showed that even in the same species there were individual differences in the various strains of *B. typhi* abd., α , β , γ , etc., so that while the antidote may be formed for one strain (α) it need not be for another (β), which then in its turn causes an exacerbation of the disease. In all probability some of the amboceptors thrown off to inhibit (α) will fit some of the receptors of (β), so that the relapse will be less severe than the original attack. We know as a matter of experience that relapses are not often fatal, at any rate in enterica.

The same line of argument will hold good for reinfections; it is then merely a question of time. The suitable amboceptors may have been already all excreted since the former attack, but it may also be that reinfection or a second attack may be produced by a bacillus of a slightly different strain.

Natural protection sometimes depends on the possession of an appreciable quantity of appropriate antidote.

We have already seen that bacteria are not digested in the alimentary canal, and it is a familiar fact that ascarides can survive the digestive juices. It has recently been shown that the body wall of ascaris contains an anti-enzyme to pepsin; and also what is more important, and interesting, that the human stomach wall contains an anti-enzyme to its own ferment. It is an obvious deduction to infer that a diminution in quantity of this antipepsin may have an etiological relation to gastric ulcer. By the production of an anti-antipeptic serum, an experimental verification of this inference would be possible.

There may be an underlying current of rationalism in the practice of periodical venesection in times gone by. The abstraction of protective bodies ought in the healthy organism to stimulate their reproduction and their over-production. In some animals there seems to be a seasonal variation in the bactericidal power of the blood; who knows but this may be so in man too, and that by instinct our forefathers may have fallen on the most appropriate season? The question admits of experimental solution, and a simple investigation would give the answer.

This line of thought suggests another mode of treatment based on Ehrlich's theory. Since infection is not possible in the absence of suitable receptors, it might be feasible to devise some means for destroying these particular receptors. The method in our present state of knowledge would not be dangerous, for we might unwittingly destroy also nutritive receptors, and do more damage than good to the patient. Perhaps it will form a part of the therapy of the future.

PREDISPOSITION.

By this term we understand an increased liability beyond the average of any individual to be attacked by a given or any disease. The existence of this tendency has long been recognized by clinicians, but by them rather surrounded with an air of mystery—at any rate, no material explanation was forthcoming.

When we speak of the thick-necked, red-faced, pig-eyed individual as being an apoplectic subject, or as predisposed to cerebral haemorrhage, we recognize certain mechanical features of his anatomy which lead to producing certain physiological or pathological results, especially favourable to cerebral apoplexy. There is probably a similar but less definite line of thought in saying that "the strumous disposition.....is indicated by light or red hair, grey or blue eyes with large and sluggish pupils and long silky lashes, a fair transparent brilliancy of skin, and rosy cheeks," or "in persons of dark, muddy complexion and harsh skin; in whom the mental and body energies are more sluggish and dull."

But description is not explanation; diathesis is not a reason.

Does Ehrlich's theory afford any explanation? We have only to suppose that there is a paucity of production of those mediators especially capable of dealing with the tubercle bacillus and its products in individuals, to whom Sir Thomas Watson's graphic description applies.

Is there any experimental foundation for assuming that individual differences of such a nature exist in the same species? The experiments of Ehrlich and others show not only that such differences exist, but that peculiar properties of the blood may be inherited.

Thus it was found that if the serum of a goat A. were injected into goat B., B.'s serum would haemolyse A.'s xanthocytes, but not C.'s or D.'s, while it might act on E.'s. Here we have clear evidence of individual similarities and differences in the same race. Experiments with the blood of man by Shattock, myself, and others have revealed similar indi-

vidual differences. Moreover Bulloch has shown that haemolysin may be transmitted from mother to offspring; and if an existing property may be so transmitted, the absence of it is even more likely to occur. Hence it seems only natural that predisposition is likely to be hereditary, and is to be met by improvement of environment and production of the deficient mediators.

Such predisposition can also be acquired, but it then shades off into the conditions to be considered under the heading of susceptibility.

SUSCEPTIBILITY.

This is very nearly allied to predisposition; it may perhaps be defined as acquired predisposition. It may be due theoretically to various causes. An absence or diminution in quantity of normal circulating mediators or the receptors for the nutritive groups may through malnutrition be left unoccupied and unguarded and consequently attacked by toxic groups, or there may be a diminution of complement.

Malnutrition is popularly and probably correctly considered to predispose towards infection, even when temporary—namely, at the time when the next meal is due. I am not aware of any direct experimental evidence in support of this hypothesis, but it can be tested experimentally.

We know that infants brought up at the breast are less susceptible to disease than infants reared on cow's milk or other artificial food, and it has been shown that the bactericidal power of the blood is deficient in the latter as compared with the former class. It is to variations in conditions of this kind that we must attribute infections by normal parasites, such as *B. coli* (appendicitis), and perhaps also by *B. typhi* abdominalis, which Koch considers a normal inhabitant of the human intestine.

As illustrating the varying susceptibility in spite of nearness of relationship I might instance the chimpanzee. We know that it spontaneously suffers from ankylostomiasis, filariasis, and trypanosomiasis. Of the first disease I have unfortunately practical experience, having lost at least one chimpanzee from it. The occurrence of the other two diseases has been recorded by Ziemann. I have been able without difficulty to infect the animal with typhoid fever as these two specimens will demonstrate. One single dose was given by the mouth. The animal was killed twelve days later.

The close relationship of its blood to man has been shown by Friendenthal and by myself. The former showed that the injection of large quantities of his own blood into a chimpanzee was not followed by any haemoglobinuria, while my own experiments demonstrated, by the injection of rabbits with human and chimpanzee blood respectively, the practical identity of the precipitins formed in each case.

In spite of this close relationship attempts to produce diseases like scarlet fever and measles in the chimpanzee have failed. It is true that on one occasion after swabbing out the throat with a swab from the throat of a case of scarlet fever an exudative tonsillitis resulted and from the chimpanzee throat the so-called *S. scarlatinae* was isolated, but I do not think the chimpanzee had scarlet fever. Apparently the chimpanzee's cells do not possess receptors for the poison of scarlet fever or measles.

Certain acquired habits are known to predispose towards disease, for example, alcoholism to phthisis. Have we any material evidence to show in what the predisposition consists? The experiments of Abbott and Bergey have shown that the administration to rabbits of alcohol diminishes the serum complement of the blood, while others have shown that it renders the rabbit more susceptible to infection by pathogenic organisms. In the case of man, diminution in the amount of serum complement in the last stages of disease has been shown on several occasions, and affords an explanation of terminal infections.

There remains a clinically very important form of acquired susceptibility. It is a matter of common knowledge that the period of immunity, if any, after an attack of pneumonia, influenza, or erysipelas is very short, and the patient often seems more susceptible than before to the disease. We have seen that the blood acquires but very feeble antitoxic or bactericidal power over the infecting organism; the stimulus to over-production seems to be very slight. Supposing this to be so, and the number of receptors reproduced not to exceed that which the cell can retain and to be less than before, the susceptibility will be increased.

SERUM DIAGNOSIS.

The existence of the agglutinins was one of the earlier results of modern investigations into immunity. They form a valuable means of identifying bacterial species and recognizing the degree of relationship between various species, whilst they have also been employed practically as a diagnostic sign in disease.* So much has been written and said about them in the past seven years, that it is hardly necessary to enter into a detailed description of their

* First performed on March 14th, 1896, and first mentioned by Gruber at the Wiesbaden Congress in April, 1896. The first publication, by Widal, was on June 26th, 1896, but he has not consented to give the date on which he first performed serum diagnosis, so that it was presumably after mine and after Gruber's utterance.

characters and production. We may mention, in passing, that the most recent work shows their probable identity with the precipitations, but not with the amboceptors, since a serum can be produced, after suitable treatment, by *B. pyocyaneus*, which possesses immunizing but not agglutinating properties.

But in the practical application of serum diagnosis various phenomena may occur which must be known and understood in estimating the value of the results. In spite of early warnings, some at once pinned their faith on the supposed infallibility of the test, and then finding that it was unable to always determine an uncertain diagnosis, became unbelievers. The agglutinins, although not identical with the amboceptors, nevertheless go roughly together with them in their rate and conditions of production under ordinary circumstances. Consequently in very severe infections, when all the cells are hard hit, and many of them succumb, the agglutinin may either be used up or not formed, so that it is but natural for the reaction to be feeble or absent until the patient is already on the road to recovery. On the other hand, in mild attacks, which may be the result of either milder infections or of greater resistance, the reaction may naturally appear sooner and be stronger. Or, again, its absence may be due to an error in diagnosis. Finally, it may be the result of faulty technique.

The following points are worthy of consideration: Agglutinins may become converted into agglutinoids. These would in this form also unite with the bacilli like the complementoids with the amboceptor, but without producing any specific effect; no agglutination would take place. The bacilli may lose their agglutinability, although retaining the power of uniting with the agglutinin—namely, their agglutinable substance loses its functional atom group. This group is comparatively unstable, so that unsuitable culture media, etc., may make the bacilli nonagglutinable, although uniting with the agglutinin. If the serum contain both agglutinins and agglutinoids, and the latter have the greater affinity for the bacteria, even if present in less quantity, they may inhibit agglutination until the serum is so far diluted as to give the agglutinins a greater chance. This explains an early observation of my own for which I was then quite unable to account, that a higher dilution would sometimes agglutinate when a lower one would not.

The agglutinable substance is partly soluble in NaCl solution, so that an emulsion of bacilli should always be made fresh, or the reaction becomes less sensitive.

PARTIAL AGGLUTININS.

This expression is used to indicate the fact that several agglutinins may exist in a serum and may have slightly different cytophile groups, so that they will react differently as regards intensity with different strains of the same bacillus. Some may even act on nearly allied bacilli. Consequently it is a matter of importance what culture is used for serum diagnosis. It is also important in using an agglutinative serum, both for the identification of a bacillus and for a serum diagnosis, that the serum should be diluted as much as possible consistent with obvious action, since in this way the misleading action of the less numerous agglutinins is eliminated.

The serum reaction is also likely to be absent in cases of erroneous diagnosis. If bacteria are otherwise nearly allied it is, at any rate, possible that they may produce symptoms having much clinical resemblance. This seems to be so in typho-coloid fever. On the other hand the relationship between the bacteria may be so close that the patient's serum may act on each in comparatively low dilutions, and the various strains may be separable only by degrees of dilution. Of course, discretion and reason must be exercised in all these cases, so that serum diagnosis requires not only considerable technical knowledge and skill, but also an acquaintance with the clinical features of the case under investigation. It is only a symptom, and its value as such in any particular case will vary like the value of any other symptom.

There is a strange gap in our knowledge of etiology regarding those diseases of which one attack produces a very lasting immunity: of small-pox, typhus, scarlet fever, measles, and others we do not know the morbid germ. It is a curious coincidence that these diseases happen to be the most infectious. I believe that the discovery of their causes would throw great light on the phenomena of immunity. Even with our present knowledge I think we can assert that they are cases of mixed infection in which streptococci play a part, but only the minor part, as often in tubercle and diphtheria. Strepto-

coccus scarlatinae seems to occur pretty constantly in the throat and in the blood of scarlet fever patients. In two cases of measles I have found in the heart blood at the necropsy a streptococcus which is always present in the throats of measles patients. But to my mind it is pretty certain that these are only accessory causes. For we know that immunity to streptococcus infection is short, and second attacks are common. Many people exposed to scarlet fever infection get sore throats repeatedly, but no scarlet fever; and streptococcus scarlatinae has been isolated from such cases.

The infectious fevers form an attractive theme for theorizing, and a yet more attractive object for investigation. Their infectivity does not seem to be all of one kind. Thus yellow fever, an attack of which also confers a long immunity, has until quite recently been regarded as highly infectious. Yet the infection is certainly not by contagion; it is transmitted by the mosquito. The pathogenic micro-organism has not yet been found. Can it be that the infectious diseases of temperate climates are transmitted in a similar fashion? It seems possible, but unlikely.

Even so, we are not any nearer either the cause of the disease nor the reason for the long immunity. But I believe the discoverer of the cause will find with it the key to the innermost temple of the Theory of Immunity.

ON THE BACTERIOLYTIC POWER OF THE BLOOD, AND ON ITS RELATION TO THE PROBLEMS OF ANTITYPHOID INOCULATION AND THE RECENT WORK OF DR. MACFADYEN.

By A. E. WRIGHT, M.D.,

Late Professor of Pathology, Army Medical School, Netley; Pathologist to St. Mary's Hospital, W.

THE publication in the form of editorials in the last two numbers of the BRITISH MEDICAL JOURNAL of the results of Dr. A. Macfadyen's researches on immunization against typhoid fever and the serumtherapy of the disease affords a convenient opportunity for bringing forward certain observations on the bacteriolytic power of the blood, and certain criticisms of Dr. Macfadyen's work. I may deal seriatim with the more important of the issues raised.

PROBLEM OF THE PROPER CONSTITUTION OF THE VACCINE.

In undertaking researches in connexion with the production of immunity against typhoid fever, the following propositions only can legitimately be taken as axiomatic:

1. The vaccine material must derive from a culture of the bacillus typhosus.
2. Owing to the risk which would attach to the employment of living cultures the vaccine material must consist either of a sterilized typhoid culture or of a constituent isolated from such a culture.
3. The vaccine material, however constituted, must be free from contaminating micro-organisms.

Every other point in connexion with the constitution of the vaccine material is a debatable point, and deserves to be experimentally investigated. Among these points is, of course, the question as to whether the vaccine material I employ—which consists of agar or broth cultures sterilized at 60° C.—constitutes the ideal vaccine material. It seems to me that the path of progress may possibly lie in eliminating from these cultures any poisonous element which may be found inert with respect to the production of immunizing substances. Reserving this point, I may here address myself to the task of considering whether Dr. Macfadyen's vaccine material—constituted as it is by triturating typhoid bacteria at the temperature of liquid air—presents advantages over the ordinary sterilized culture which I employ.

In view of the results I have obtained in the course of an experimental inquiry into the fate of typhoid bacteria introduced into the blood and lymph, it appears to me that the question I have raised above may be answered in the negative. I find that when an ordinary twenty-four-hour-old typhoid culture—supposing it to contain not more than about 1,000,000,000 typhoid bacteria in the cubic centimetre—is mixed in a capillary tube with an equal quantity of normal human serum (blister fluid), and is digested with this serum or lymph for thirty minutes at blood heat, considerably over 99 per cent. of the typhoid bacteria are dissolved by the