Unfortunately, the fact that the great war has found the men of literature and of science amongst the most active and polemical writers on either side, goes to show that the highest grade of mental cultivation has little influence on the elemental characters of man's nature.

Thus while the Central Powers have gone so far as to strive to prevent their medical literature reaching their enemies' hands, the conditions of war have furthered a most intimate association between the medical services of the armies allied in the same cause. Not only has a brotherly alliance existed, unbroken throughout by any national jealousy, but the same lines of thought and the same tide of action and reaction in practice has been observable in all. The reports of the Inter-Allied Conference on the Treatment of Wounds furnish an excellent illustration of these facts.

Amongst the surgeons of the Allied nations an increased spirit of fraternity and intimate coöperation has certainly flourished. Just as the armies of the different States have placed their resources of every kind at the disposal of each other, so the workers in medical science have pooled their knowledge and growing experience, and readily received and adopted variations or advances from whatever source they might emanate.

THE FUTURE STATUS OF THE CONSULTING SURGEON.

Those who were privileged to take part in the recent campaign will at once recognise that although omissions have no doubt been made in sketching this outline of the duties of the consulting surgeon, yet it embodies in the main what has been the practice in the British Army, and a system which has been appreciated and even imitated in the armies of our Allies. Still, as far as I am aware, the system remains founded upon usage during the war, it has resulted from a process of development in successive steps, and it is no doubt capable of further regularisation and organisation.

The authoritative pronouncement of Sir Alfred Keogh¹ affords sufficient grounds to absolve me of any intention of wishing to magnify the office of the consultant, either at the expense of the regular service, or of the splendid body of men for whom the nation was in the main part indebted for the hard work of the campaign. It should be realised, however, that the position assigned to the consultant with the Army corresponds in dignity and importance with that of the professor in a medical faculty, and his power of influencing the whole character of the work is equally great. We cannot doubt that the experience gained will be utilised by clearly defining what the status and duties of the consultant will be in the future, but I would submit that these should be laid down while the facts that should decide them are still fresh in the minds of the powers that govern the Army Medical Service.

It is much to be desired that the principle introduced in 1903 of inviting civil consultants to form a part of the staff of the Military Hospital at Millbank should undergo further development, and be but a step towards the permanent association of civil practitioners with the work of the military hospitals throughout the service. Thus a connexion between the two branches of the profession in times of peace would be established which could not fail to simplify and render more efficient the change which must follow mobilisation in the case of any war of magnitude.

CONCLUSION.

These remarks upon the duties of the consulting surgeon cannot be closed without allusion, however brief, to the charms and pleasures of the position. For the first time in his professional career he attains an opportunity of practising surgery for the sake of surgery alone, a position which many a man with the responsibilities of the civil practitioner has longed for as the impracticable ideal. A routine occupation is suddenly transformed into a free and varied existence, with periods of strenuous work it is true, but also others in which abundant opportunity is found to ponder over the many interesting problems which arise, and, moreover, a wealth of material which allows the acquisition of a practical experience which many years of civil practice would not suffice to acquire.

Lastly, the favourable conditions which are afforded of cultivating a close relationship with colleagues. Happy as the association of the consultant may be with those with whom he works in civil life, they cannot approach the free

intercourse of mind with mind which obtains in life in the field. Freedom of discussion, the constant sharpening of wits in encounters with young and ardent workers eager to assume the position of the pioneer, the social life and the charm of entering on equal terms a society such as brings back memories of youthful days are but some of the pleasures only to be fully appreciated by those who have enjoyed the privilege of experiencing them.

No less happy are the somewhat novel relations which establish themselves between the consultants, and between the consultants and the officers of the regular service, which it is to be hoped form a presage of the future, a continuing co-partnership founded upon a common aim and mutual appreciation.

DETOXICATED VACCINES,

WITH SPECIAL REFERENCE TO GONORRHOEA, NASAL AND BRONCHIAL CATARRH, AND INFLUENZA.

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(1) Prefatory Note.

EARLY in 1917 Brevet Colonel L. W. Harrison, K.H.P., D.S.O., asked me to make up a large amount of ordinary gonococcal vaccine for use in the army. He stated that his experience with the ordinary vaccine had been very promising and he thought it deserved an extensive trial on a large number of patients. Since that time about one million doses of this vaccine have been sent out from the laboratory, and extensive researches have been made in the course of which I devised a method of removing the toxins from germs, without thereby altering their specific antigenic properties. This is obviously a discovery of great importance and I feel confident that it will mark a great advance in the science of vaccine therapy.

It is well known from thousands of well proved experiments that the living tissues of man and animals possess the inherent power of manufacturing specific antistances against germs when attacked or irritated by them. This peculiar power is so highly specialised that the antistances produced acts only against the infecting germ and not against any other species. In other words, the tissues react specifically and produce a special antistance towards each bacterium. An "antigen" is a substance which when injected into the living tissues stimulates the production of an antibody towards itself. Each species of germ (alive or dead) is, therefore, a "specific antigen." The greater the amount of antigen injected into the tissues, the greater is the quantity of antistance produced.

Unfortunately, germs hitherto have been so toxic that only very small amounts of their dead bodies (vaccine) could be injected into the tissues, and so the amount of antistance produced by these preventive inoculations was limited by the toxicity. With the discovery, however, of "detoxication" (removal of the poison) I have been able to inject without toxic symptoms doses of vaccine from ten to one hundred times greater than was ever dared before, with the result that a much greater amount of immunity is developed.

I am deeply grateful to Colonel Harrison for much encouragement and for the unselfish interest he has displayed towards my researches. I desire also that credit may be given to my able assistants, Sergeants A. W. Denney and C. H. Holland. They enthusiastically assisted me, working long beyond their specified hours for over two years, throughout the whole period of this research. I wish particularly to express my thanks to the former (A. W. Denney) for his highly skilled assistance in laboratory technique. Finally, I am much indebted to my clinical colleagues, Dr. A. Allport and Mr. C. H. Mills, for their friendly coöperation.

(2) Introduction.

When I first commenced to make and use gonococcal vaccine I was more or less obsessed with the idea that to get good results the dead germs should be as fresh and as unchanged as possible. In consequence, young cultures not more than 24 hours old were employed, and the emulsions were made up with 0.5 per cent. NaCl containing

¹ British Journal of Surgery, 1916, No. 13, iv., 3, 4.

0.5 per cent. carbolic acid. I even avoided heating the vaccine. It is quite unnecessary, since the gonococcus dies rapidly in the saline carbolic fluid. At this time I made every endeavour to turn out a vaccine in which the gonococci were quite discrete and showed no signs of autolysis. It was found that a considerable amount of disintegration of the germs gradually occurred in the saline carbolic fluid. To solve this difficulty an investigation was made into the cause of the autolysis.

(3) *Cause of Autolysis of the Gonococcus and the Solubility of the Germ in Alkali.*

I discovered eventually that the phenomenon of autolysis was almost purely a question of alkalinity. In an acid medium autolysis was inhibited almost indefinitely, whereas in an alkaline medium it occurred very rapidly. In other words, the gonococcus was extremely soluble, even in weak alkali, but was entirely insoluble in weak acids. In consequence, ever after this I made up the vaccine in a solution of 0.5 per cent. acid sodium phosphate (NaH_2PO_4) and 0.5 per cent. carbolic acid.

This rapid solution of the gonococcus in a weak alkaline solution such as N/10 or N/20 sodium hydroxide aroused my interest very considerably, so much so that I attempted to find out some facts regarding the chemistry of the germ substance, and further experiments were made with other species of bacteria to ascertain whether or not they behaved in a similar manner. It was found that the *Gonococcus*, *Meningococcus*, *B. typhosus*, *B. Friedländer*, and *B. influenzae* Pfeiffer were all very soluble in weak alkalies. The influenza bacillus was the most easily dissolved of all. On the other hand, comparative insolubility was characteristic of all Gram-positive organisms tested—namely, *Staphylococci*, *Pneumococci*, *Streptococci*, *Diphtheroids*, &c. These germs resisted the action of normal sodium hydroxide. Some of them, however, showed signs of solution in 10 per cent. NaOH, and all dissolved in antiformin (15 per cent. NaOH and liquor sodæ chlorinatæ). As a rule, however, it required warmth and prolonged action of the antiformin to cause complete solution. Practically all Gram-positive germs dissolved in antiformin in 12 hours if kept in the incubator at 37.5°C.

It is not an invariable rule, however, that Gram-positive organisms are less soluble in alkali than those which are Gram-negative. On one occasion a very Gram-negative bacillus which grew profusely was isolated from the nasal secretion of a patient. This bacillus was even more resistant to alkali than the Gram-positive organisms mentioned above. Some species of coliform organisms were very soluble in alkalies, other species, however, required antiformin. On investigating the chemical nature of these alkaline germ solutions it was found that a precipitate was thrown down by the addition of excess of acid. The precipitation, however, did not take place until the solution was definitely acid, so it was possible by the gradual addition of acid to bring the solution to the neutral point without precipitation.

(4) *Discovery of Method of Removing Toxin.*

In the course of these chemical investigations I found that when an N/10 alkaline solution of gonococci was precipitated by normal hydrochloric acid the neutralised supernatant fluid was strongly toxic in character and caused a severe reaction when injected subcutaneously into the human subject. It was, indeed, more toxic than the actual precipitate of the gonococcus substance itself. When the latter was collected, redissolved in alkali and reprecipitated with acid, the supernatant fluid gradually lost its toxicity and the precipitate itself became comparatively non-toxic after this process had been repeated about six times.

To put it shortly, the gonococcus and indeed all germs consist of stroma and toxin. Both constituents are soluble in alkali, but the stroma (the bulk of the germ) is thrown out of solution by an acid leaving the toxin in solution. More recently I found that the toxin could be removed by simply washing the precipitate repeatedly with a weak acid such as 0.5 per cent. acid sodium phosphate containing 0.5 per cent. carbolic acid.

Some germs precipitate more readily from alkaline solutions than others when acid is added. The *Gonococcus*, *Streptococcus*, *Pneumococcus*, and the *B. influenzae* are precipitated very readily. On the other hand, *B. Friedländer*, *B. typhosus*, and *B. coli* can only be precipitated with great difficulty. A centrifugal machine is practically indispensable

for the work. Germs which sediment or settle readily are easily precipitated from alkaline solutions and, vice versa, those which settle slowly from emulsions are difficult to precipitate.

(5) *The Chemical Nature of the Stroma Precipitate and the Supernatant Toxin.*

Attempts were made to elucidate the chemical nature of the stroma and toxin of the gonococcus. Both were found to be colloid substances, since the alkaline solutions were incapable of passing through a dialysing capsule. Even filtration through a Berkefeld filter caused adsorption of a considerable quantity of this colloid substance from the alkaline solution of the stroma. Solutions of gonococci did not give a definite biuret reaction, indicating that they are not composed of highly organised albumin. The precipitate of stroma was insoluble in sodium carbonate and also more or less insoluble in alcohol, ether, and acetone. This proved that the substance was not a fatty acid. Salkowski's colour test seemed to indicate the presence of cholesterol, but ordinary cholesterol is quite insoluble in alkali.

Samples of the stroma precipitate and the supernatant toxin were given to Dr. Nierenstein (bio-chemist, Bristol University). He found traces of nitrogen in the toxic portion, but little signs of it in the stroma deposit. It would appear, therefore, that the gonococcus is composed of a substance of a rather unusual and unknown character. The chemical analysis, however, has been rather indefinite as the quantities used were too small. Further investigations are required before any reliable statements can be made.

(6) *The Antigenic Value of the Stroma Precipitate and the Toxin.*

It was found that a neutral solution of gonococci prepared by dissolving the germ in normal NaOH, then adding sufficient acid to bring it to the neutral point, was very excellent as an antigen when used in the complement-fixation test. It was less anticomplementary and more powerful antigenically than an emulsion of the undissolved germs. This proved that the specific characteristics of the gonococcal germ substance were not altered by being dissolved in normal caustic soda. Indeed, certain German observers maintained that an antiformin gonococcal antigen was superior to an emulsion of the gonococci in the complement-fixation test. This shows that even very strong alkali does not destroy the specific antigenic characteristics of the germ substance.

Again, if the supernatant toxic fluid is neutralised it is found to act as a good antigen. The non-toxic precipitate when dissolved and neutralised also acts as a very good antigen. It is evident, therefore, that both stroma and toxin are antigenic. From the practical point of view, however, it would appear that the stroma is more antigenic than the toxin, since it is capable when injected into animals of stimulating the formation of a larger quantity of anti-substance in the animal inoculated.

During the past ten years and more there has been a considerable controversy regarding the endo- and exo-toxins of germs. The exotoxins are those which are excreted by the germ. Endotoxins, on the other hand, are not excreted but remain enclosed within the germ stroma. The most recent researches have shown that antiserums can be developed against the exotoxins by injection of the latter into animals. Thus, good antitoxic sera have been produced against the exotoxin of *B. diphtheriae* and *B. tetani*. On the other hand, no definitely successful antiserum has, so far, been produced against any of the endotoxins, with the exception perhaps of antimeningococcus serum (Gordon, 1918).

Most workers have maintained that antiserums cannot be developed against the gonococcus toxin by injection of the latter into animals. Wells,¹ who has investigated the literature on the subject, finds little evidence that antiserum is produced against the endotoxin of any germs. It is agreed that the toxins of the *Gonococcus*, *Meningococcus*, *B. typhosus*, &c., consist of endotoxin. Indeed, the majority of the toxins of pathogenic organisms are considered to belong to the endo type.

In view of this concurrence of scientific opinion it appeared to me that little or no advantage could be gained therapeutically by the injection of powerful poisons like endotoxin when no antiserum formation could be induced in the system towards them. On the other hand, practically every investigator is satisfied that antibodies such as agglutinins,

bacteriolysins, precipitins, and complement-deviating substances are produced against the bodies of germs by inoculation of the latter (dead or alive) into man and other animals. Hence the therapeutic value of vaccines. The injection of a vaccine (dead germs) acts for the good by stimulating the formation of the specific antistances in the system of the injected person.

(7) *The Importance of Large Doses of Vaccine if Satisfactory Immunity is Desired.*

Vaccines are highly poisonous on account of their toxins, which are usually endotoxins. In consequence one can only dare to inject a limited quantity. The average dose is some 5 to 100 million germs. This, to any person except a bacteriologist, would appear to be a very large dose. Germs, however, are so minute that a dose of 100 millions represents only an almost invisible speck of germ substance. On regarding this minute speck with the naked eye one finds it hard to believe that its injection into a human being could confer any large amount of immunity to the germ. The toxins, however, are so extraordinarily poisonous that this minute dose may cause an intense local and general reaction, often accompanied by malaise and fever.

It is because of this intense poison or toxin that the dose is so small. The majority of workers on vaccine therapy are satisfied that these small doses of dead germs are of value both in the treatment and prevention of disease. Some maintain that the germs should be freshly prepared from recently isolated cultures. Others say that they should not be heated, and some say that they deteriorate on keeping. Finally, certain clinicians believe in autolysed vaccines injected intravenously. Efforts have been made also to make the germs less toxic by sensitisation after the method of Beuredka.² Nicolle³ claimed to have rendered the gonococcus less toxic by growing the germ on a special medium and by making up the vaccine in a solution of sodium fluoride. On the other hand, a few clinicians have failed to find any good arise from vaccines and, indeed, some maintain that they are harmful because of their toxic nature, whereby they aggravate the symptoms of the disease and lower the vitality of the patient.

From a minute examination of the literature, however, one is forced to note that the bulk of opinion is favourable. The scientific laboratory experiments show that antistances are produced in the system as the result of inoculations by a vaccine. More recently the extraordinary success of antityphoid inoculations has proved beyond all doubt that vaccines are destined to be of the very greatest value.

Why has antityphoid inoculation been so successful? The success, in my opinion, is due to the relatively large dose injected. Thus, where the normal dose of many vaccines is some 5 to 100 millions, the dosage of antityphoid inoculations is for the first injection 1250 millions and for the second 2500 millions. The typhoid bacillus is a comparatively large germ and the actual amount of germ substance used in this inoculation is markedly visible to the naked eye. It is quite an appreciable quantity.

Torrey⁴ found that no detectable immunity was produced in guinea-pigs towards the gonococcus when the dose injected was less than 1/16th of the fatal dose. When doses, however, equal to 1/8th to 1/12th of the fatal amount were injected quite a considerable quantity of antistance could be detected in the blood. This indicated that more immunity was produced by the larger doses. The problem obviously points to the development of some method whereby larger doses might be given without harmful effects. To attain this end the toxin must necessarily be removed. When removed there is no harmful effect produced by introducing into the tissues large quantities of dead bacteria.

Of maximum importance is the fact that these dead germs minus the toxin have not lost their specific antigenic power in the process of detoxication. This is evident from the fact that the endotoxins themselves have little antigenic property when injected into the tissues.

(8) *The Production of Antistances is Nature's Method of Dealing with Attacks by Germs.*

If we ask ourselves the question why does a person recover from a disease, we must admit, as a rule, that it is not due to any drug, but due to an inherent power in the

system which has successfully overcome the germ which caused the symptoms. This inherent power is the faculty possessed by the infected tissues of generating anti-substances towards the germ. These antibodies are agglutinins, precipitins, bacteriolysins, and complement-deviating substances.

When an individual is attacked by a germ the issues are threefold. (a) The germs may multiply so rapidly that the tissues are completely overcome and paralysed by the toxins before antistances have had time to develop. In such circumstances the patient dies. (b) If the patient is able to survive the attack for some days the infected tissues of his body are, as a rule, able to completely eradicate the disease by the generation of an overwhelming amount of antistance to the germ in question. (c) Sometimes a compromise takes place. A kind of balance is established wherein sufficient antibodies have been produced to keep the germs in abeyance, but not sufficient to completely destroy them. When this occurs a mild and chronic condition is established, and the patient may go about in moderate health quite unaware that he is a carrier of the disease and a source of danger to others. Thus, we have typhoid carriers, malaria carriers, dysentery carriers, and, doubtless, also influenza carriers. I have found the influenza bacillus in the sputum of persons who were apparently well.

Carriers are, unfortunately, by no means rare. The majority of patients who recover from a given disease eradicate the germ completely. The antistances which brought about the cure remain in the system for some considerable time, usually some three months to several years. As a rule, it is gradually eliminated and finally disappears. When this occurs the patient is again more or less susceptible to a fresh attack.

(9) *The Artificial Production of Antistances by Means of Vaccines in Order to Prevent or Cure Diseases.*

When a vaccine of a given germ is injected under the skin, say, of the arm, the local tissues at once react and commence to destroy the dead substance of these germs by the manufacture of specific solvents and precipitins. These antistances are produced in excess and circulate in the blood of the person. If large doses are injected frequently, sufficient of the antibodies are developed in the circulation to render the patient quite insusceptible to attack by the germ in question.

When a large quantity of detoxicated vaccine is injected under the skin a large amount of immunity is produced without any bad symptoms arising such as would have occurred if the toxin had been present. In the course of a disease one does not care to inject large quantities of a toxic vaccine when the patient is already suffering severely from the poisonous effects of the live germ with which he is infected. With the detoxicated vaccine, however, injections into the subcutaneous tissues away from the seat of infection can, without increasing the toxic symptoms, compel the healthy tissues to manufacture specific antistances. In other words, during an attack, say, of bronchitis, due to the *Micrococcus catarrhalis*, an injection of the detoxicated vaccine of this germ into the upper arm would compel the tissues of the upper arm to take part in the struggle against the bronchitis and to produce specific antistances locally which are carried into the circulation and brought to the theatre of war in the chest. Thus it is within our power to compel any healthy tissue in the body to produce antistance to a germ attacking elsewhere without getting any aggravation of symptoms by the injection of toxin.

Napoleon, in a conversation with Dr. Warden on board the *Northumberland*, which carried him to St. Helena, drew a simile between a physician and an army general. Both, he said, were confronted by similar problems. The enemy had to be driven out of a citadel without, if possible, destroying that citadel, and this was often a very difficult matter. Strong drugs like mercury might destroy the enemy, but he maintained that large doses also injured the body. So it is with vaccines. We may stimulate healthy tissues to produce antistances to help to drive the germs from the diseased localities, but if too much toxin is injected along with the vaccine the diseased tissues and the body as a whole may be injured thereby. With the discovery of detoxication it would appear that a new method of attack has been devised whereby this danger can be avoided.

(10) *Mode of Detecting Antisubstances in the Blood. Proof that Large Amounts are Produced by the Use of Detoxicated Vaccine.*

Antisubstances to germs can be detected in the blood by the agglutination test, by the precipitin test, or by the complement-fixation reaction. The last is probably the most delicate test of the three.

If a given serum contains antibodies to the gonococcus, for example, that serum when mixed with a concentrated solution of gonococci will result in the formation of a precipitate. This constitutes the precipitin test. The complement-fixation reaction, however, is much more delicate. It is really an indirect, but very accurate, method of detecting the precipitate which forms as a result of the union between an antigen and its specific antisubstance.

In order to test scientifically the relative value of detoxicated vaccine and ordinary toxic vaccine in the production of immunity I carried out a large number of complement-fixation tests in four parallel series of patients. Clinical observations were carried out simultaneously by the same clinician.

Series A.—Gonorrhoeal patients who received no vaccine treatment.

Series B.—Gonorrhoeal patients treated with small doses of ordinary gonococcal vaccine.

Series C.—Gonorrhoeal patients treated with larger doses of ordinary gonococcal vaccine.

Series D.—Gonorrhoeal patients treated with large doses of detoxicated gonococcal vaccine.

The amount of complement deviated in the presence of antigen and serum was estimated weekly in each patient for a period of five to six weeks, and sometimes for a much longer time.

The immunity was measured by the amount of complement fixed. One minimum hæmolytic dose of complement fixed represented 1 unit of immunity. The fixation of

Before vaccine. 7th day. 14th day. 21st day.

CHART I.—Average amount of complement fixed with no vaccine treatment (A), after treatment with ordinary vaccine (B, C), and with detoxicated vaccine (D).

2 M.H.D. represented 2 units of immunity and so on. I was surprised at the extraordinary accuracy of this test, as was shown by the marked regularity of the graphs when the results were charted. The total number of cases treated scientifically in this manner amounted to about 150. The results were shown to an experienced actuary, and he considered that they were more convincing and more reliable evidence of the efficiency of vaccines than even many thousands of cases treated clinically. He maintained that clinical and statistical evidence lacked homogeneity, and that this detracted considerably from its value in spite of the large numbers involved.

It would take up too much space to give the complement-fixation chart of each case. Chart I., however, suffices to show that the immunity is highest in the vaccine-treated cases, and the marked superiority of the detoxicated vaccine over the smaller doses of the ordinary toxic vaccine is very apparent.

Series A, in which the patients received no vaccines, showed on the average some 3 units of immunity acquired naturally in the course of the disease.

Series B received ordinary gonococcal vaccine in doses of 5 to 100 millions and developed about 4 units of immunity.

Series C received ordinary gonococcal vaccine in doses of 25 to 200 millions and developed an average of 5 units of immunity.

Series D received detoxicated gonococcal vaccine in doses of 2500 to 10,000 millions and developed, as a rule, 8 to 12 units of immunity.

I attempted at first to watch the clinical results myself, and noticed that those cases which developed the highest amounts of complement-deviating substances recovered most

rapidly. Those which showed little capacity of developing such immunity were the slowest to recover.

The capacity of developing antisubstance in response to vaccines varied greatly in different patients. About 1 out of every 15 cases showed a low capacity in that they failed to develop more than about 6 units of immunity in spite of large doses of detoxicated vaccine amounting to a total of 50,000 million gonococci or more. It was noticed that such cases were slow in recovering.

The task of carrying out simultaneously the serological and clinical observations was too great, however, for one individual, and Colonel Harrison kindly placed Captain David Lees, D.S.O., in charge of the clinical part of the investigations. I wish to congratulate this officer on the very thorough manner in which he performed his work, and he has consented to follow my paper with an account of his clinical observations and studies.

(11) *Inoculation of Normal Individuals with Gonococcal Vaccines.*

Ordinary gonococcal vaccine was injected into several normal persons who had never suffered from gonorrhoea and who gave completely negative complement-fixation reactions. In these cases it was found by repeated tests that no detectable complement-deviating substances were developed in the blood after an injection of 100 millions of the ordinary gonococcal vaccine, followed by 200 millions six days later. On the other hand, a dose of 5000 millions of detoxicated gonococcal vaccine induced the formation of sufficient antisubstances in the blood to give a double positive reaction, and a total amount of 10,000 millions developed a triple positive reaction in another normal person whose blood was previously negative. Moreover, the dose of 200 millions of ordinary gonococcal vaccine produced malaise and fever in the normal subject, whereas the symptoms arising from a dose of 5000 millions of the detoxicated vaccine were scarcely noticeable, and no fever was induced.

(12) *Length of Time that Antibodies Remain in the Blood.*

With regard to the two normal individuals mentioned above, the double positive serum reaction became again negative after a period of four months, and the triple positive case became negative after a lapse of six months. A gonorrhoeal subject who showed a triple positive reaction was forced up to ten positive after two months' treatment with detoxicated gonococcal vaccine. The vaccine was then stopped and complement-deviation tests were done every 14 days for the next six months. The results (Chart II.) showed a gradual fall in immunity from 10 positive to four positive during this period—that is to say, one unit of immunity was lost each month.

CHART II.—Effects of vaccination in regard to formation and disappearance of antisubstance.

It will be observed that the rise and fall of immunity is indicated by a more or less bell-shaped curve. Thus the antisubstance inclines to rise slowly at first, then more rapidly. So with its disappearance it falls rapidly from a height, then tails away more slowly from the lower level.

Chart III. shows the very rapid rise in antibody produced by detoxicated vaccine. This patient had suffered from chronic gonorrhoea for over a year, but with the high rise of antisubstance the gonococci entirely disappeared.

(13) *The Complications of Germ Infections.*

In gonorrhoea, as in most other bacterial diseases, the original infecting germ which causes the disease is apt to be followed and complicated with a variety of other germs which are able to settle down on the devitalised tissues. Thus very many cases of gonorrhoea, and more especially chronic gleet, show in the purulent discharge such organisms as staphylococci, diphtheroids, pneumococci, &c. Even after the gonococcus is completely eradicated these secondary organisms may remain behind and carry on the trouble in a mild form for a very long period of time. In such cases a pure gonococcal vaccine is insufficient, and obviously a mixed vaccine of the secondary organisms must be given. It has been found that these mixed vaccines are of great value in clearing up such cases, and most clinicians have spoken most favourably of the results obtained by them in very chronic cases.

CHART III.—Rapid rise in antisubstance after injections of detoxicated vaccine; in all, 56,500 millions.

(14) *Researches on Nasal and Bronchial Catarrhs.*

I have been markedly susceptible to so-called "influenza" attacks for many years. In 1917 I commenced to study the bacteriology of my own bronchial and nasal secretions.

A severe attack (three days in bed) in January, 1917, showed a pure infection with the *Micrococcus catarrhalis*. An ordinary autogenous vaccine of this germ was made and a total of 330 millions was injected during the next six weeks. In March I developed measles, accompanied with some bronchitis, and the *M. catarrhalis* was again cultivated from the sputum. Two more doses of the catarrhalis vaccine (60 millions), combined with 20 millions pneumococci, were again injected. In May, during a slight cold, both these germs were cultivated from my sputum. Inoculations were again commenced until a further total of 340 millions catarrhalis and 240 millions pneumococci had been given during that month.

No further catarrhs occurred, and towards the end of September I commenced to immunise myself for the winter with the same mixture of catarrhalis and pneumococci. A total of 480 millions of the former and 360 millions of the latter were injected during October, November, and December. On the Christmas Day I developed a severe nasal catarrh, with some fever. A culture grew the pneumococcus and the *M. catarrhalis*. A fresh autogenous vaccine was made of both, and 220 and 380 millions respectively of each were injected by the middle of January, 1918. On the 19th of that month I had a slight nasal cold, and numbers of catarrhalis germs were found in the secretion. During February and March a further total of 300 millions of each was injected, and no further catarrhal attacks developed.

Thus from January, 1917, till March, 1918, I was inoculated with a total of 1790 millions catarrhalis and 1680 millions pneumococci. This failed to give me a satisfactory immunity towards these germs, though I must say that while during 1917 I had three very bad influenza colds, during 1918 I had only one attack, which was unusual for me.

In the summer of 1918 I discovered the method of detoxication, and I prepared separate detoxicated vaccines of all the various catarrhal germs, including the *Pneumococcus*, *M. catarrhalis*, *B. Friedländer* and *Septis*, and during the influenza epidemic I also made detoxicated vaccines of Pfeiffer's bacillus and the hæmolytic streptococci which had been obtained from fatal cases. The cultures of the latter were obtained from the R.A.M.C. College,

Millbank, through the kindness of Colonel D. Harvey. In October, 1918, I inoculated myself twice with a mixture of detoxicated Pfeiffer, streptococci, and pneumococci, giving a total of 5000 millions (1000 millions Pfeiffer, 500 millions streptococci, and 3500 millions pneumococci). In November I developed a nasal catarrh which proved to be due to Friedländer's bacillus. 500 millions of detoxicated Friedländer were immediately injected, and the catarrh was completely cut short in one day. A fortnight later I developed a cough and from the sputum I grew practically a pure culture of *M. catarrhalis*. 500 millions of this germ (detoxicated) were injected immediately, and the attack was cut short in a remarkable manner.

These last observations proved most conclusively that a prophylactic vaccine for bronchial and nasal catarrh was useless unless it was a mixed vaccine containing every species of germ giving rise to such attacks. In consequence I made a compound detoxicated vaccine composed of a mixture of *Pneumococci*, *M. Catarrhalis*, *B. Friedländer*, *B. Septis*, *Streptococci*, and *B. Influenzæ* (Pfeiffer), containing 10,000 millions per c.cm. I have had no trace of catarrh since inoculating myself with this mixture. First dose 1500 millions, second dose 3000 millions, third dose 3000 millions. These doses caused no inconvenience except some local redness and tenderness.

About 150 persons have been inoculated with two doses in this manner, and as no influenza or catarrhs have been recorded so far amongst them except one very mild case, I have considerable hope that this inoculation will prove of marked value in the prevention of these affections. Also during a catarrhal attack this compound inoculation has showed a marked power of bringing the infection to a rapid termination.

As already mentioned, I have come to the conclusion that for success in immunisation large doses of 1000 million germs and upwards must be given, and this has been rendered possible by the process of detoxication described. At any rate, my experience with the small doses of ordinary *M. catarrhalis* vaccine given frequently during 1917 and 1918 showed that these were insufficient to give any very definite immunity. I have considerable hope, however, from my experiments during 1919 that two or three doses of the detoxicated mixture given in October, and a similar course administered in January (total 9000 to 15,000 millions) will be able to cause the development of sufficient immunity to provide a very considerable protection against attacks by the germs in question.

Ordinary mixed catarrhal vaccines have been in use for some years, but they are so toxic that it is dangerous to administer doses greater than a total of 200 millions of the mixture. If such a dose were given every week in the year this would only amount to a total of 10,000 millions.

(15) *Notes on the Present Influenza Epidemic.*

If Pfeiffer's bacillus combined with the hæmolytic streptococcus and the pneumococcus is the cause of the present fatal epidemic, I have no hesitation in saying that inoculations with these germs must convey a certain amount of immunity. There would appear, however, to be some considerable controversy and doubt as to the exact nature of the causal organisms. Some maintain that the germ is a filterable virus.

I have had no opportunity of carrying out any direct bacteriological investigation into fatal cases. Nevertheless, I would like to say that one of the strains of hæmolytic streptococci sent to me from the R.A.M.C. College, Millbank, proved to be a remarkably small organism, certainly the smallest germ I have ever seen, and I feel confident that it would have been capable of passing through a filter. This small streptococcus, moreover, was most exceedingly toxic.

It was difficult to cultivate requiring a very fine human plasma agar medium such as I use for the gonococcus. The Pfeiffer bacillus I found refused to grow on the very best varieties of plasma agar because the presence of hæmoglobin was absolutely essential. This latter organism also required moisture and practically refused to grow when the hæmoglobin agar became somewhat dry. The conditions suitable for Pfeiffer's bacillus are more or less the opposite to those required for the gonococcus. The latter organism grows best on a dry plasma agar medium containing glucose, and the former grows best on a moist hæmoglobin agar containing no glucose.

If the epidemic is primarily due either to the Pfeiffer's bacillus or the small streptococcus mentioned, or both, I have no hesitation in saying that one would frequently fail to isolate them by cultures from patients because of the exact conditions necessary for their growth. I would suggest that inability to isolate these organisms in certain cases may be due to errors in the culture medium employed. At any rate, this possibility requires to be excluded before one can definitely claim that the epidemic is due to some organism of an entirely different character.*

(16) *Final Researches on Detoxicated Vaccines.*

A detoxicated vaccine can be used in two forms. It can be made up in the form of a neutral or slightly alkaline solution, or else it can be made up with a weak acid, in which case it is an insoluble precipitate which requires to be shaken well before use. In the majority of cases in Series D described above, the soluble variety was used, and this was injected intramuscularly into the buttock. It was noticed, however, that 10,000 millions caused a transitory drop in the immunity of the patient as estimated by the complement-deviation test. This temporary negative phase with reduction of antisubstances continued, as a rule, for about 20 hours, after which the immunity again commenced to rise.

After ascertaining this fact it occurred to me that it might be better to inject the insoluble precipitate. It is conceivable that an injection of the soluble form might rapidly penetrate into the blood stream and have the immediate effect of combining with existing antisubstances in the circulation, thereby neutralising them. If precipitate, however, were injected it would tend more to remain local, and without neutralising existing antibody in the circulation it would irritate and stimulate the local tissues to produce further quantities of specific immune substances. In consequence I now prefer to inject the precipitate which is made up in a solution of 0.5 per cent. acid sodium phosphate (NaH_2PO_4) containing 0.5 per cent. carbolic acid. The inoculation is made subcutaneously. Cases of gonorrhoea treated by this latter method have done remarkably well, and have shown a rapid rise in the amount of complement-deviating substance in the blood.

Before concluding, I would like to point out that immediate miraculous results must not be expected from any vaccine. It is inconceivable that an injection of dead germs should cause an immediate alleviation of symptoms. Indeed, the first result is a negative phase lasting some 20 hours, during which time the symptoms may be aggravated. After this time antisubstances gradually commence to develop during the next 7 to 14 days. Vaccines should not be injected more often than about once every three to five days. The results obtained are gradual and progressive. One of the great advantages of vaccine treatment is that the immunity is worked up to a high level, and on this account a relapse is a very rare occurrence.

A certain number of disappointments must be expected, since for some reason still obscure certain individuals seem to have very little faculty of developing antisubstances even when large doses are injected. This phenomenon is markedly noticeable also when rabbits are injected with sheep's corpuscles for the purpose of producing hæmolysins towards the latter. Certain rabbits develop an enormous amount of antisheep corpuscle substance, whereas others develop very little. No one, so far, has been able to explain why this difference should occur.

No doubt in the near future, when the conditions which govern the formation of antisubstances are more fully elucidated, we may find it within our power to produce very rapidly even 20 units of immunity. When we have attained this knowledge and power I feel assured that the complete mastery of practically all bacterial diseases will be the result.

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* Since this paper was sent in for publication the evidence recently accumulated by various workers seems to show that Pfeiffer's bacillus was not the primary cause of the great influenza epidemic. It would appear that the causal organism was a filter-passer, but whether this new germ has any relationship to the minute streptococcus mentioned above I am unable to state.

DETOXICATED VACCINES IN THE TREATMENT OF GONORRHOEA:

THE VALUE OF THE COMPLEMENT-DEVIATION TEST IN CONTROLLING THE TREATMENT AND ESTIMATING ITS THERAPEUTIC EFFECT.

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DURING recent years the treatment of gonorrhoea and its complications has aroused much controversy. Very few workers have satisfied themselves that anything like a satisfactory treatment has yet been attained.

Early in 1916, while working in No. 9 Stationary Hospital, B.E.F., I tested on parallel series of cases different modes of treatment, both local and general, and was very much impressed with the results in a large series of cases of a mixed vaccine known as staphgon. The vaccine contained in each c.cm. 150 million staphylococci and 50 million gonococci, and was prepared by Major Dawson, R.A.M.C., and Captain McWhirter, R.A.M.C., pathologists to the hospital. Definitely noticeable were: (1) the mild course of the case treated ab initio with vaccine; (2) the absence of complications; (3) the smaller number of relapses. These impressions were confirmed by Captain Lumb¹ in a large series of cases.

Value of Vaccine Therapy in Gonorrhoea.

Among the many workers, both in this country and abroad, who have tried vaccine therapy in gonorrhoea, there is an almost unanimous consensus of opinion as to its good therapeutic effect in the complications of gonorrhoea. Broughton-Alcock² in Paris, Semionov,³ Dopter and Pauron,⁴ Culver⁵ in America, and Asch⁶ in Germany have all testified to its good therapeutic effect in this type of case.

The most satisfactory results have been obtained by: (1) increasing the dose to a point at which it was almost toxic (W. G. Brett⁷); or (2) preparing the vaccine so as to reduce its toxicity, either by sensitising it after the manner of Besredka,⁸ or of Howarth,⁹ with the former of which methods Cruveilhier obtained excellent results, or by growing it on a special medium as did Nicolle and Blaizot,¹⁰ whose results and also those of Remlinger,¹¹ were consistently good with a vaccine so prepared and known as Dmégon.

Workers who used ordinary stock vaccines—e.g. Wright, Harrison, Asch, Sachs, and many others—have contented themselves with smaller doses, 5 to 25 millions, initially, and working up to 150 or 250 millions, preferring rather to have small reactions, both general, local, and focal, and never to increase the dose if reaction was great. In America they have preferred higher doses, 50 to 100 millions being average doses in acute cases, while in chronic cases they go as high as 500 millions, and state that in chronic gonorrhoeal arthritis lesser doses have no action at all. The more promising results of American workers are due chiefly, I think, to the larger dosage, and to the fact that in later years they have controlled the dosage and the intervals between doses, not only by clinical observation, but also by serological tests.

From close clinical and pathological observation, I feel convinced that on account of its toxicity our dosage has been too small to produce a large immunity response. The cases which did not give an immunity response to the injection of a vaccine in the early stages were those in which the substance injected, by reason of its toxic nature, more or less destroyed the antibody-producing power of the tissues which nature had just begun. Those in which there was a larger and immediate response to vaccine treatment were the cases in which nature had already taken up the task and the tissues were already well accustomed to producing anti-substances in quantity and only required some additional stimulus to produce more.

This is seen if we compare the serological tests of the two cases of the same duration—say, an epididymitis of six days and an anterior urethritis of six days' standing. The first will almost invariably show 1 to 3 units of anti-substance, while the latter never shows more than $\frac{1}{2}$ to 1 $\frac{1}{2}$. This is borne out by almost all workers who concede that vaccines are of use in the complications of gonorrhoea, but not markedly in early cases of uncomplicated urethritis.