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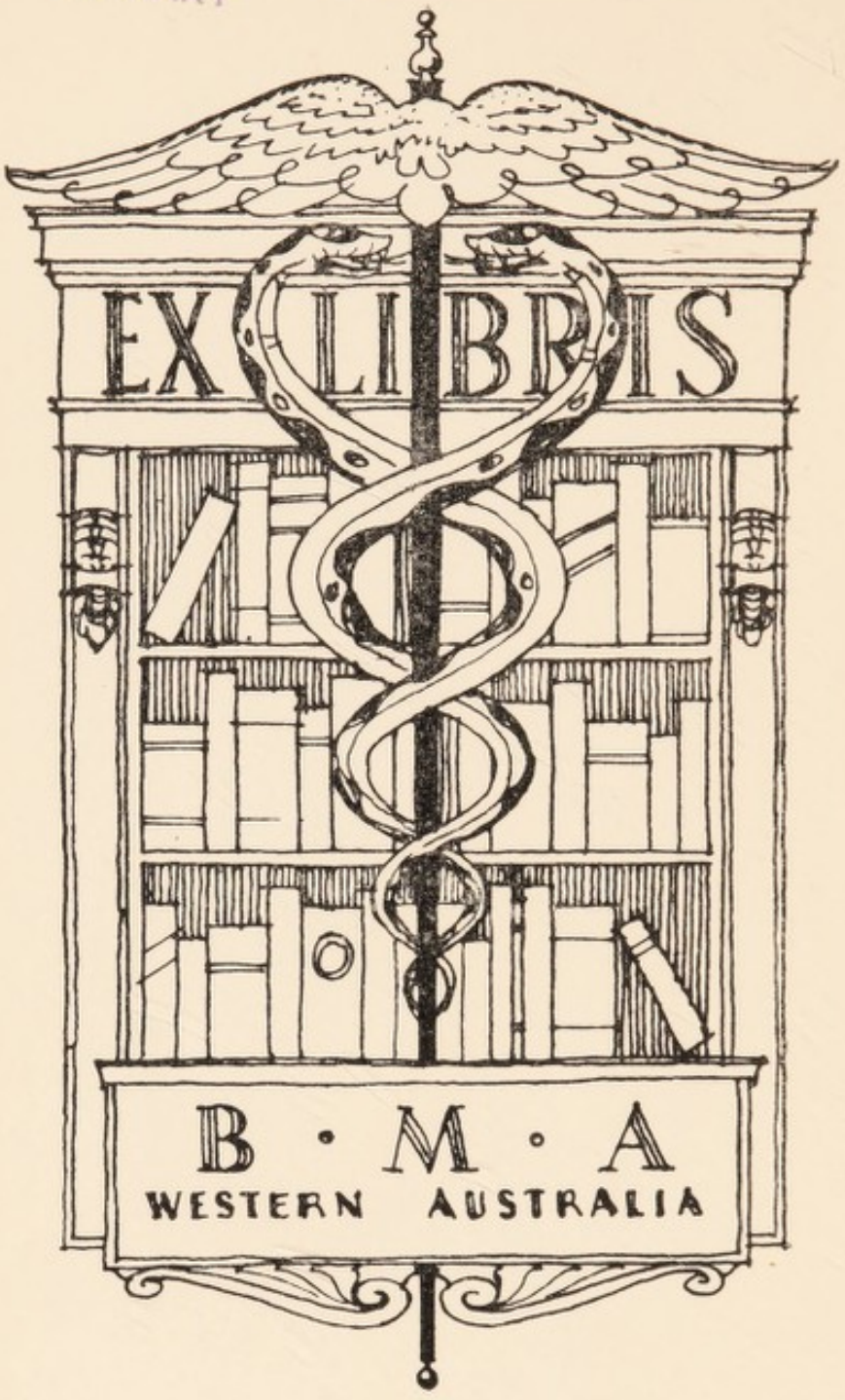
Modern Medical Monographs

BACTERIAL VACCINES AND THEIR POSITION IN THERAPEUTICS

LEONARD S. DUDGEON



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MODERN MEDICAL MONOGRAPHS

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Professor of Medicine, University of London

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PREFACE

THIS monograph was written by request to provide a short account of the uses of bacterial vaccines in therapeutics. No attempt has been made to review the literature of this vast subject, as so many books have adopted this line of action already. I have attempted to place on record my direct personal observations, based on twenty years' experience of the vaccine treatment of acute and chronic bacterial infections. There is little doubt that many of the views and conclusions recorded in this short monograph on vaccine therapy will not be in agreement with the much too optimistic statements so frequently made on this subject. No one who has studied vaccine treatment seriously can question its value, but it is equally important to understand its limitations. The selection of cases suitable for vaccine treatment requires much experience, while the problem of dosage, which is different in every case, is still far from understood. In prophylaxis vaccine therapy has done great work; in fact, one of the chief lessons learnt, but not sufficiently appreciated, during the Great War was the remarkable efficiency of "typhoid" vaccine.

I have endeavoured to put my views as fairly as possible, and as the observations are entirely personal I am alone responsible for the many controversial statements expressed. It is hoped, however, that some help will be given to those who wish to study this interesting

subject and apply it for the treatment of bacterial infections.

I wish to offer my sincere thanks to Dr. A. L. Urquhart, a colleague in the Department of Pathology, St. Thomas's Hospital, for reading the manuscript and proofs, and for his many valuable suggestions.

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CHAPTER I

THE PRINCIPLES OF ACTIVE IMMUNISATION WITH BACTERIAL VACCINES

THE immunity which man and animals possess against certain bacterial toxins is known as the natural immunity, and this natural immunity varies to a considerable degree among individuals. As a result of the infections which we acquire during childhood or adult life, active immunity is established. The degree of active immunity which follows recovery from different infections varies considerably. An immunity which persists through life *usually* follows smallpox, measles, typhoid fever, scarlet fever, and some of the other exanthemata ; while such acute bacterial infections as gonorrhœa, pneumonia, and erysipelas appear to afford only a very short temporary immunity, or more frequently no active immunity is established. In those infections in which active immunisation is produced, it does not of necessity follow upon a severe illness ; it may occur from a very mild infection.

The active immunisation produced by direct smallpox inoculation, which was practised for hundreds of years in the East, and the production of vaccinia by inoculation of cowpox into man, which Edward Jenner showed would afford protection against smallpox for many years, gave

to us the first conception of active immunisation, or, in other words, the immunity produced by direct inoculation with a virus.

The study of scientific immunisation dates from the work of Louis Pasteur. Those who wish—and it should be the wish of every intelligent man and woman—to know how Pasteur built up the science of bacteriology, and demonstrated the principles of active immunity, should read the Life of Louis Pasteur, by René Vallery-Radot. In 1880, while Pasteur was studying chicken cholera, he made an observation which proved to be the scientific foundation of active immunity. The facts are recorded in his Life, by Vallery-Radot,[1] as follows : " A chance, such as happens to those who have the genius of observation, was now about to mark an immense step in advance and prepare the way for a great discovery. As long as the culture flasks of the chicken cholera microbe had been sown without interruption, at twenty-four hours' intervals, the virulence had remained the same ; but when some hens were inoculated with an old culture, put away and forgotten a few weeks before, they were seen with surprise to become ill and then to recover. These unexpectedly refractory hens were then inoculated with some new culture, but the phenomenon of resistance recurred. . . . And while hens who had never had chicken cholera perished when exposed to the deadly virus, those who had undergone attenuated inoculation, and who afterwards received more than their share of the deadly virus, were affected with the disease in a benign form, a passing indisposition. Sometimes even they remained perfectly well ; they had *acquired immunity*."

[1] Vallery-Radot, René (1902) : " The Life of Louis Pasteur." Translated from the French by Mrs. R. L. Devonshire. Constable, London.

The idea of preventing disease by inoculating animals with microbes which had been so modified or attenuated as to produce immunity without the animals acquiring the disease opened up a wide field for investigation. It was only a few years later (1885) that Pasteur treated a human subject with his modified rabies virus. The wide application of the treatment and prevention of disease in the human subject with bacterial vaccines so as to establish active immunisation is due largely to the work of Sir Almroth Wright and his colleagues.

Pasteur used the word "vaccine" for emulsions of dead or attenuated bacteria, as Jenner had employed the word "vaccination" for his inoculation with cowpox virus.

It is usual nowadays to employ the term "bacterial vaccines" for emulsions of bacteria prepared for the *active* immunisation of man or animals, as opposed to the *passive* immunisation produced by means of anti-sera. The only difference between bacterial vaccines and cowpox vaccine is that in the former we have a suspension of microbes in saline, or other fluid, which have been cultivated on artificial media, while with cowpox vaccine, as the virus cannot be cultivated outside the body for purposes of satisfactory immunisation, it is suspended in the tissue lymph.

In the preparation of vaccines every effort is made to keep the microbes as near the living state as is compatible with safety, so as to avoid as far as possible reducing the immunising properties. Bacterial emulsions are killed in various ways, of which heat and chemicals are perhaps the most commonly employed. Bacteria can be attenuated by cultivation at an abnormal temperature, by exposure to air or light, by drying as in the case of the rabies virus, by treating the microbe with specific immune

anti-serum (Besredka's method), and by extracting the microbe with chemicals. The employment of the living microbe has been attempted, but this method of inoculation is in the experimental stage, and should not be employed for the human subject.

What is the Purpose of Active Immunisation with Bacterial Vaccines ?

Active immunisation is employed either to prevent disease in the healthy subject or for the treatment of patients already suffering from bacterial infections.

The bacterial vaccines are antigens, or substances which stimulate the activity of the tissue cells and body fluids. As a result of the inoculation of a vaccine, substances are formed which can be demonstrated in the blood serum, such as agglutinins, opsonins which are concerned in phagocytosis, precipitins and bacteriolysins. The same substances are formed during infection with the living microbe as are produced in the healthy subject from active immunisation with a vaccine of the same microbe. Further, the substances which appear in the blood of the inoculated individual are largely specific for the microbe used in the preparation of the vaccine. The formation of protective substances, such as agglutinins, opsonins, precipitins, and bacteriolysins, is evidence of immunisation, and the fact that these substances are formed in varying amounts depends upon circumstances, such as the response of the tissues of the inoculated individual, the nature of the microbe, the method of preparing the vaccine, and the dosage employed, but unfortunately the presence of all these substances, even in large amounts in the blood, is not necessarily an indication of the patient's resistance to a bacterial infection.

CHAPTER II

THE PRODUCTION, STANDARDISATION AND DOSAGE OF BACTERIAL VACCINES

VACCINES employed in this country are usually made by killing the organisms with heat, or, less frequently, with chemicals. The method of examining infected material obtained from various diseases in man is briefly referred to at the commencement of the various chapters, but suffice it to mention here that pure cultures of the organisms are obtained by plating, and then single or mixed vaccines are made according to circumstances. The usual practice is to subculture the selected colonies on to agar, or other suitable media, incubate at 37° C. for twenty-four to forty-eight hours, usually twenty-four hours, and then to add sufficient sterile saline to the agar growths to make a satisfactory emulsion. This can be readily accomplished by rolling the culture tube between the hands, using the necessary amount of agitation. The method I employ for freeing bacterial emulsions from clumps and extraneous matter is to filter through sterile fine linen placed in sterile glass funnels.

The methods adopted for the sterilisation of the emulsions are : (1) heat ; (2) chemicals.

(1) *Heat.*—The bacterial emulsion is put into a closed glass receptacle in a water-bath at a temperature varying from 50°–60° C. Probably the most satisfactory temperature is from 50°–55° C. for thirty to sixty minutes, but to ensure the sterility of some bacteria a temperature of 58° C. or 60° C. for one hour is necessary. The tempera-

ture of the water and the length of time required for sterilisation depend to some extent on the density of the bacterial emulsion, and also on the microbe itself, as is shown by the fact that some strains of bacteria are killed much more readily than others. Pneumococci, for instance, are easily killed, while *S. aureus* and *B. coli* are much more resistant to heat ; *B. paratyphosus B* is more resistant than *B. typhosus*.

After the bacterial emulsion is removed from the water-bath it is subcultured on to agar, or other suitable medium. These subcultures are incubated at 37° C., and examined at intervals of twenty-four and forty-eight hours, to ensure the sterility of the vaccine.

(2) *Chemicals.*—Dreyer suggested formalin for sterilising bacterial emulsions, and recommends its use in the cold. I have found that these emulsions can be more rapidly killed if they are incubated at 37° C. for twenty-four hours in a closed vessel after the formalin is added. I have killed my bacterial emulsions during the last eleven years with 0·1 per cent. of formalin in sterile saline. The emulsions are kept in sterile glass bottles closed with waxed corks at 37° C. for twenty-four hours, as by this method it has been found that the emulsions are dead at the end of this period. I employ the same technique for all bacterial emulsions, and it is only occasionally that they have been found to be resistant to this method of sterilisation ; when this has occurred it has been due to extreme density of the bacterial suspension.

Formalin-killed vaccines are tested for sterility, as are the heat-killed vaccines. Much denser emulsions than are necessary for ordinary purposes can be killed with formalin, if we raise the temperature, *e.g.*, to 45° C., and slightly increase the strength of the formalin.

Before the War I employed heat-killed vaccines only,

but since 1915 I have used formalised vaccines prepared as already described.

Other chemicals can be used for sterilisation, such as 0·5 per cent. phenol, but I prefer formalin to any other.

When the bacterial emulsion is proved to be sterile, it is standardised, and then diluted to the required strengths with normal saline containing 0·25 per cent. phenol. Some bacteriologists test the sterility of bulk emulsions, such as are required for prophylactic inoculation against typhoid fever, cholera, and certain other infections, by injecting mice and guinea-pigs, so as to exclude the possibility of contamination with tetanus bacilli before these vaccines are issued.

Standardisation

Various methods have been introduced from time to time for this purpose, notably Wright's, in which equal quantities of human blood and bacterial emulsion are mixed together ; film preparations of the mixture made on glass slides are then stained, and the relative number of bacteria to red cells counted. The number of human red cells per cubic millimetre is known, and, therefore, the strength of the vaccine is readily arrived at. Other means have been introduced, *e.g.*, (*a*) direct counting of the bacterial emulsion with the hæmocytometer ; (*b*) counting the colonies on suitable plate preparations ; and (*c*) by certain opacity tests.

The method of standardisation which I personally consider to be the most satisfactory and by far the most simple, and which I now use entirely for this purpose, we owe to the painstaking work of Brown and Kirwan.[1]

[1] Brown, H. C., and Kirwan, E. W. O. (1915) : " Standardisation of Bacterial Suspensions by Opacity," *Indian Journal of Medical Research*, vol. ii., p. 763.

This method depends on the opacity of the bacterial suspension when compared with graduated standard tubes of increasing density from 1 to 10. Cunningham and Timothy [1] in 1924 compared the opacity tubes of Brown [2] with hæmocytometer readings which are now recorded for a large number of the pathogenic bacteria employed in vaccine treatment. It is unnecessary to describe this method in greater detail, as the opacity tubes and tables of corresponding bacterial strengths can be obtained in a very convenient form from Messrs. Burroughs & Wellcome. It is well to recognise, however, that emulsions standardised by some of the other methods mentioned give entirely different readings when estimated by Brown's standard tubes.

By means of Brown's tubes bacterial emulsions can be readily standardised in a few minutes, and no expert knowledge is required.

Dilutions

Bacterial emulsions are diluted, as already stated, to the required strengths with normal saline containing 0·25 per cent. phenol. I usually prepare two dilutions for therapeutic purposes, one containing about 40 to 200 millions of the microbe to the cubic centimetre, according to the organism, *e.g.*, in the case of the pneumococcus 40 millions per cubic centimetre, and in that of *S. aureus*, 150 to 200 millions per cubic centimetre. The other contains 800 to 2,000 millions per cubic centimetre. By this means suitable dilutions are prepared for the early and later stages of the treatment.

[1] Cunningham, J., and Timothy, B. (1924): "A Comparison between the Numerical Content of Certain Bacterial Suspensions obtained by the Hæmocytometer Method and Brown's Opacity Tube," *Indian Journal of Medical Research*, vol. xi., p. 1253.

[2] Brown, H. C. (1919): "Further Observations on Standardisation," *Indian Journal of Medical Research*, vol. vii., p. 238.

When compound vaccines are used the bacterial emulsions are mixed according to the required strengths.

Vaccines which are put on the market are often sent out in coloured glass capsules, which denote the strengths of the bacterial emulsions. It is the usual custom to employ vaccine bottles containing 25 and 50 c.c., which are closed with sterile rubber caps waxed with paraffin. Vaccines should be stored at room temperature in the dark. I seldom use a vaccine which is more than six to eight months old, but some observers consider vaccines satisfactory at a much greater age.

The injections should be made subcutaneously into a different area of tissue on each occasion. In my experience, the local and general effect produced by a formol-killed vaccine is less than that produced by a heat-killed vaccine. Reactions are seldom encountered with any of the formol-killed vaccines until large doses are administered.

When massive quantities of vaccines are required, as for prophylactic purposes, the microbes are grown in large flasks of agar, and the growth is washed off with formol saline in the usual way. In the East, during the Great War, we found that flat-faced whisky bottles served for this purpose most effectively.

When large quantities of pneumococcal and streptococcal vaccines are required, I grow the bacteria in beef broth containing glucose, to which small quantities of sterile human serum are added just before the culture tubes are inoculated, as by this means abundant growths are obtained. The growth in the liquid media is centrifugalised at high speed, the supernatant fluid is completely removed, and the bacterial deposit emulsified in formalised normal saline. The same procedure is then adopted as already described for agar emulsions. Sufficient growth

can also be procured on various solid media, *e.g.*, saline egg slopes and inspissated blood serum.

Micro-organisms which auto-agglutinate or emulsify only with great difficulty can be shaken with sterile glass beads on an electric shaker so as to obtain a uniform suspension of the bacteria, while recently, Bensted [1] has recommended emulsifying the bacteria in hypertonic (10 per cent.) saline solution.

Sensitised Vaccines

Besredka and Metchnikoff [2] prepared emulsions of living bacteria which were mixed with specific immune sera until they were sensitised. These sensitised bacterial emulsions were employed for prophylactic and for therapeutic purposes. It was considered that "vaccines" prepared in this manner would produce little or no negative phase, or local, or general reaction. It was also urged in favour of these "vaccines" that large doses could be injected, that the bacteria were readily phagocytosed, and that the necessary immune substances were rapidly produced within the body. "Vaccines" prepared in this manner appealed to many workers, because it was believed that a negative phase did not occur after the injection of this specially prepared material, and therefore the most important disadvantage of the ordinary vaccines was removed. Subsequent workers employed sensitised dead bacteria instead of sensitised living microbes so as to avoid any risk which might occur from injecting live organisms, more especially as it was claimed that the sensitised dead bacteria were equally effective.

[1] Bensted, H. J. (1926): "Serological Investigations with *B. pestis*," Laboratory Meeting, Sect. Tropical Medicine, Roy. Soc. Med.

[2] Besredka and Metchnikoff (1911 and 1913): *Ann. de l'Inst. Pasteur*, vol. xxv., pp. 193, 867; vol. xxvii., pp. 597, 607.

The technique employed for the sensitisation of bacterial emulsions is briefly as follows: specific immune serum, previously heated to destroy the complement, is added to the bacteria which have been grown for twenty-four hours on agar or other suitable medium, and the mixture is allowed to stand for varying periods, usually one hour at 37° C., and all night at 0° C. The emulsions are then centrifugalised, the deposit washed in saline containing 0·1 per cent. formalin, and the suspension killed in this formol saline. The further procedure is similar to that already described for ordinary formol-killed vaccines.

My own experience has failed to convince me that there is any advantage in the use of sensitised vaccines over vaccines prepared on the lines advocated by Wright. The enthusiasm for sensitised vaccines was very considerable in the early days of this method of treatment, but, as is so often the case in "medicine," the optimism shown at the outset seriously detracted from any advantages that this method of treatment might have possessed. Kolmer [1] sums up the question of sensitised vaccines in the following sentence: "The superiority of sensitised killed vaccines is more theoretical than practical on the basis of actual experience."

The Negative Phase

This term was employed by Wright for the depressed immunity following the injection of a large dose of typhoid vaccine. For many years attempts have been made to find a method by which the negative phase following the injection of any vaccine could be avoided and thereby the dosage correctly regulated.

[1] Kolmer, J. A. (1923): "A Practical Text-book of Infection, Immunity and Biological Therapy." W. B. Saunders & Co., Philadelphia and London.

Dosage

The most difficult problem to decide in vaccine treatment is the correct dosage, as each individual appears to have his or her response to vaccines, just as patients vary in their response to a living microbe. As a result of a large amount of laboratory work on the examination of the phagocytic and bactericidal powers of the blood, and the strength of the agglutinin and precipitin contents of the serum, I have come to the conclusion that there is no laboratory method at the present time by which we can obtain satisfactory evidence of a patient's resistance to infection, or of the dosage to be employed in the treatment of acute and chronic infections by vaccines. Attempts to obtain a practical and reliable method from examination of the blood which would serve to indicate the dosage have not given satisfactory results. For these reasons it is necessary to rely on clinical evidence until a satisfactory working system is devised.

"Tuberculin"

Kolmer has summarised the treatment of tuberculosis by tuberculin briefly, as follows: "That while tuberculin is not a specific 'cure' for tuberculosis, any more than hygiene, diet, and climate are cures—it helps to arrest the disease and is in general a useful factor in the treatment of certain types of the disease."

It is the custom to refer to the various preparations of the tubercle bacillus as "tuberculins," whether they are extracts or suspensions of the bacillus. It was owing to the fact, as found by Koch, that the tubercle bacillus contained substances which inhibited the repair of the tissues, that he attempted to obtain extracts of the bacillus free from such substances, but possessing immunising properties. The number of such preparations which have been put on the market from time to time is very con-

siderable, and unfortunately each new preparation is proclaimed as superior to all previous preparations. The chief tuberculins are as follows :

1. Koch's old tuberculin (O.T.). This contains the soluble products from the growth of the bacillus in broth. It is used for diagnostic purposes in man and animals, and for treatment.

Large shallow flasks containing 5 per cent. glycerin broth are inoculated with human tubercle bacilli and grown at 37° C. for six to eight weeks, so that an abundant growth on the surface of the medium is obtained. The growth in glycerin broth is then sterilised and concentrated by heat to one-tenth of the original volume, while the glycerin remains unaffected. The bacilli are then removed by filtration of this concentrated fluid through a porcelain candle. The resulting clear brown filtrate (O.T.), which keeps indefinitely, is now ready for use.

2. Koch's new tuberculin is known as T.R.

This tuberculin, also introduced by Koch, is prepared by growing virulent cultures of human tubercle bacilli in glycerin broth for about six weeks ; the bacilli are then removed by filtration and dried in a vacuum. One gramme of the dried tubercle bacilli is ground in an agate mortar, 100 c.c. of distilled water are added, and the mixture centrifugalised. The clear fluid which separates off is known as Tuberculin O. The sediment is dried, ground in an agate mortar, and mixed with a small quantity of water, centrifugalised, and the fluid decanted. The process is repeated until no bacterial sediment remains. All the fluid resulting from this process is collected, except the first (T.O.). The total volume should not exceed 100 c.c., and to this 20 per cent. of glycerin is added. In each cubic centimetre there should be 2 mgm. of solids, representing 10 mgm. of dried tubercle bacilli.

3. Koch's bacillary emulsion (B.E.).

In the preparation of B.E. the bacilli are grown as for old tuberculin, and then filtered off, ground, *but not washed*. To one part of the pulverised bacilli 100 parts of distilled water are added, the whole is emulsified, and an equal part of glycerin is added.

4. Denys introduced a tuberculin preparation known as " B.F.," which is prepared in a manner similar to Koch's old tuberculin, except that the bacillary free filtrate is not heated or concentrated.

This form of tuberculin has been widely used for the treatment of tuberculosis.

Numerous other methods introduced by various workers for the preparation of tuberculins are beyond the scope of this monograph. In recent methods heat, such as is used in the manufacture of old tuberculin, is avoided, and the bacilli are extracted with chemicals, with the idea of removing the toxic, necrotic, and anaphylactic substances from the tuberculin, while it is hoped that only the immunising substances will remain.

Cultures of tubercle bacilli emulsified in normal saline and sterilised by heat or chemicals are also employed as in the preparation of other bacillary vaccines. These vaccines of tubercle bacilli can be prepared, if time permits, from the patient's own microbe. They are also known as bacillary emulsions, although distinct from the B.E. of Koch, the manufacture of which has already been referred to.

Dilutions

Dilutions of tuberculin are made with carbolised (0·25 per cent.) normal saline. They must be freshly prepared, and should on no account be stored for long periods. The dilutions are made with sterile glass pipettes, and it is important to cleanse the mouths of the bottles con-

taining the pure tuberculin with a strong antiseptic before any of the tuberculin is withdrawn. The dilutions are put into the ordinary sterile glass vaccine bottles.

The Tuberculin Reaction.—The reactions to tuberculin are as follows :

1. A constitutional reaction indicated by loss of weight, rapid pulse, pyrexia, and such general symptoms as insomnia, gastro-intestinal disturbances and headache.

2. Local reaction at site of inoculation, which varies from a slight inflammatory reaction to a severe inflammation with adenitis.

3. Focal reaction in and around the tuberculous process. This reaction is of the utmost importance, but is in no way peculiar to tuberculosis, as it occurs in all bacterial infections. Experience has shown that a severe constitutional reaction may be accompanied by a very slight focal reaction, and the converse is equally true.

Tuberculin is non-toxic for individuals who are not tuberculous, and produces no reactions however injected. In tuberculous subjects very small amounts of tuberculin may elicit a marked effect with hyperæmia and reaction of the tissues in and around the tuberculous focus. A similar reaction may occur from auto-inoculation in tuberculous subjects.

The idea of tuberculin administration is to produce such tissue reaction as will ultimately lead to fibrosis of the tuberculous focus.

A tolerance to tuberculin may develop during the course of tuberculin treatment, as shown by the fact that at the outset an injection of 0·0001 c.c. of old tuberculin may produce a local, general, and focal reaction, but after a prolonged course of tuberculin carefully regulated, 0·01 c.c. or even larger doses may fail to elicit a response. On the other hand, the converse occurs so that tolerance

to increasing doses is lost, and it is necessary to return to the smaller doses employed at the commencement of treatment.

Although at the present day the severe reactions which Koch aimed at, and obtained in the treatment of tuberculosis with tuberculin are avoided, yet there are two schools whose views differ as to degree of reaction which may be safely permitted during the course of tuberculin treatment. It is obvious that some focal reaction must be produced, or no effect can occur from tuberculin, but the ideal line of treatment is that which will produce the smallest amount of focal reaction sufficient to excite tissue stimulation of a mild degree. Such a result can only be obtained by treating every case as a distinct unit, and by the employment of very small doses at the outset, which should be gradually increased.

Constitutional disturbances, such as pyrexia, increased pulse rate, and loss of weight, depend upon severe focal disturbances, and must be avoided.

The initial dose of any tuberculin preparation for adults should be about 0·0001 c.c., but if pyrexia is present then a still smaller initial dose is desirable. The injections are given subcutaneously.

Some observers give a series of *intracutaneous injections* so as to ascertain the degree of reaction obtained with varying strengths of tuberculin. Treatment is commenced with the smallest dose of tuberculin which just excites a cutaneous reaction.

Tuberculin injections have to be continued as a rule for considerable periods lasting over many months, but it is during the first two or three months that the most important information is obtained as to the probable value of tuberculin treatment.

The Indications for Treatment with Tuberculin.—Kolmer

considers that tuberculin treatment may be employed in the following circumstances :

1. Patients afflicted with incipient tuberculosis.

2. Advanced and moderately advanced cases may be given tuberculin, if the nutrition is satisfactory, the febrile reaction mild, the pulse not very rapid, and if the patients are at rest. Old fibroid cases with fair nutrition are especially suitable.

3. Cases of tuberculosis of the lymphatic glands, skin, and special organs may be benefited by prolonged and careful tuberculin therapy.

4. Cases of latent tuberculosis with indefinite physical signs, especially the children of infected families who are physically below par and show tubercular hypersensitiveness.

CHAPTER III

AUTOGENOUS VACCINES, STOCK VACCINES, AND NON-SPECIFIC PROTEIN THERAPY

It was one of the chief principles in vaccine therapy that an autogenous vaccine prepared from the microbe which caused the infective process, should be employed whenever circumstances permitted. When vaccine treatment was considered advisable in acute infections, sufficient time might not be available for the preparation of the autogenous vaccine, due to such causes as gross contamination of the infective material, or when the infection was known but the material for bacteriological examination was not available. Under such conditions stock vaccines were employed. Apart from these circumstances, autogenous vaccines were the rule. Of recent years, however, there has been a tendency to employ stock vaccines without due consideration of the relationship of the infecting microbe to that from which the stock vaccine had been prepared. This fact is of considerable importance, as so many mistakes in vaccine therapy are due to failure to recognise that such differences do exist. Let us consider for one moment the infections caused by *S. aureus*, which may be among the most serious to which the human subject is liable, or may be of a more or less trivial nature. The infection may be in any organ or tissue of the body, yet cultures of *S. aureus* obtained from various sources are so closely related that I am not aware at the present time of any reliable means by which substantial differences can be shown to exist

between the various strains. In *S. aureus* cases, therefore, as far as my experience goes, autogenous vaccines and stock vaccines are of about equal value; although exceptional cases occur for which autogenous vaccines are necessary. The question, therefore, of specific treatment with autogenous staphylococcal vaccines is answered by the bacteriological evidence available at the present time. Now, if we consider *B. coli* infections we find that cultures of *B. coli* obtained from the urinary tract show wide differences when the cultural, hæmolytic and serological relationships are compared; similar differences are found among strains of *B. coli* obtained from other sources.

It is essential to realise that the commonest infections of the urinary tract are due to bacilli showing distinct bacteriological characteristics, and although these bacilli are grouped together under the general term *B. coli*, the fact that they are really not identical necessitates the use of autogenous vaccines in the treatment of the infections which they cause.

The bacteriological differences between strains of *S. aureus*, on the one hand, and *B. coli*, on the other, serve to form a contrast when discussing the advantages of stock and autogenous vaccines. Another organism of great interest in connection with this question is *B. typhosus*. As far as I am aware, strains of *B. typhosus* are similar from whatever part of the world they have been isolated; although certain minor differences have been described, yet, it is a fact that a typhoid vaccine prepared from one strain protects the population against typhoid fever in any part of the world.

The strains of the majority of bacteria employed in vaccine therapy, however, show cultural, hæmolytic, and serological differences which necessitate the pre-

paration of autogenous vaccines whenever this is possible.

In my opinion, therefore, autogenous vaccines should be employed for the treatment of bacterial infections, so as to stimulate the tissues to produce specific antibodies. But if an infection is caused by certain microbes, such as *S. aureus* and *B. typhosus*, then stock vaccines may be tried for the reasons already stated.

The use of stock vaccines without full appreciation of these circumstances is generally due to lack of knowledge of the subject, or it may be that the principles of non-specific protein therapy are regarded as of equal or of greater importance than specificity. Hans Zinsser [1] expresses himself very forcibly on the subject of stock vaccines. He says : " The random use of stock vaccines without laboratory diagnosis and without control is, of course, an entirely unjustifiable procedure." The treatment of acute generalised bacterial infections is dealt with in Chapter V., but as the subject of specific immunisation is now under discussion it may not be out of place to refer to the same author's remarks on the vaccine treatment of acute bacterial infections. He says : " In acute infectious diseases any effect that has been claimed for vaccines, we believe, has been due to the non-specific reactions " . . . " and in no sense to a specific immunising effect of the injected bacteria." This view, coming from such an experienced investigator as Hans Zinsser, opens up the question as to the value of the treatment of bacterial infections by non-specific proteins, more especially as remarkable results have sometimes been obtained with stock vaccines in acute and chronic infections, when distinctive differences have been recognised between the microbe causing

[1] Zinsser, Hans (1923) : " Infection and Resistance," 3rd ed. The Macmillan Co., New York.

the infection and that employed for preparation of the vaccine. We must realise, however, that there is no known method by which it is possible to judge whether non-specific protein therapy will be curative, or ineffective, or harmful. Ill-effects are, however, especially likely to occur with protein shock.

Those of us who have had many years' experience with specific immunisation are able to judge with a very fair degree of accuracy the prospects of success or failure with autogenous vaccines, while the value of specific prophylactic immunisation in the case of typhoid fever is proved beyond question.

The treatment of bacterial infections with non-specific vaccines has led to the use of non-specific proteins for this purpose. As far as I am aware, non-specific proteins have been employed only for the treatment of bacterial infections, and not for their prevention. The literature on the subject of non-specific protein therapy is overwhelming, but we are only concerned here with the question as to whether it should be employed instead of autogenous vaccines. The general reaction following the intravenous, intramuscular, and subcutaneous injections of foreign protein in the form of a vaccine varies considerably according to the clinical condition of the patient, the dosage, the method of administration, the nature of the vaccine, and last, but not least, on other circumstances which have yet to be understood before the remedy can be regarded as more than empirical. Clinical symptoms which may follow the injection of a non-specific vaccine, given with the idea of promoting tissue reaction, are a chill, or even a true rigor, and pyrexia which may reach 104° F., with an increase of the symptoms from which the patient was suffering. Weichart [1] considers that a

[1] Weichart, W., and Schrader, E. (1919): "Ueber Unspezifische

stimulation of the body cells follows the intravenous injection of a non-specific protein, with an increased formation of specific anti-bacterial substances, or a generally increased resistance to intoxication. In my opinion, however, non-specific vaccines should be employed for the treatment of bacterial infections, more especially when given intravenously with the idea of promoting protein shock, only after full consideration of each individual case and of the risks that may occur. Let us think of ourselves as patients rather than as non-specific protein administrators! It would appear that Kolmer's [1] views on the subject of non-specific protein therapy are in close agreement with those which I have expressed above, as shown by the following quotation from his work on Infection and Immunity: "It potentially is a dangerous therapy by reason of the damage that may be caused by injudicious selection of the agent and error in dosage."

Leistungssteigerungen," *Munch. med. Wchnschr.*, vol. lxvi., No. 1, p. 289. Weichart, W. (1920): *ibid.*, vol. lxvii., No. 1, pp. 91–93.

[1] Kolmer, J. A. (1923): "Infection, Immunity and Biologic Therapy," 3rd ed. W. B. Saunders, Philadelphia and London.

CHAPTER IV

ON PROPHYLACTIC INOCULATION

Typhoid and Paratyphoid Fevers

The preventative treatment of typhoid and paratyphoid fevers is now so well known and fully established that it has become a recognised plan to be inoculated against these infections before visiting foreign countries, either for long or short periods, where the sanitation is known to be defective and cases of typhoid or paratyphoid fevers are not infrequent. There is no doubt that men women and children should be inoculated if they intend to visit or remain in the East and in certain parts of Europe. Statistics conclusively prove the wonderful success obtained with "T.A.B." inoculation during the Great War, yet, in my opinion, it has never been sufficiently realised how much the world is indebted to Sir Almroth Wright for introducing this method of protection against typhoid fever. Pfeiffer and Kolle [1] demonstrated in 1896 the effects of the immunisation of two volunteers with heat-killed typhoid vaccine, while Wright [2] recorded the results of his early experimental observations at a somewhat later date. Subsequently he introduced a method for the protection of troops, which he further

[1] Pfeiffer, R., and Kolle, W. (1896): "Experimentelle Untersuchungen zur frage der Schutzimpfung des Menschen gegen Typhus abdominalis," *Deutsch. med. Wchnschr.*, vol. xxii., p. 735.

[2] Wright, A. E., and Smith, F. (1897): "On the Application of the Serum Test to the Differential Diagnosis of Typhoid and Malta Fever," *Lancet*, vol. i., pp. 656–659. Wright, A. E., and Semple, D. (1897): "Remarks on Vaccination against Typhoid Fever," *Brit. Med. Journ.*, vol. i., pp. 256–259.

improved in conjunction with Leishman and other workers. It is this method which is practised throughout the world at the present day.

Although it has been suggested that improvement in hygiene and sanitation are as much responsible for the decrease of typhoid fever as is immunisation, those of us who worked in some of the Eastern war areas during the Great War obtained absolute proof of the remarkable efficiency of T.A.B. inoculation. Every man can be inoculated, but one cannot inoculate the principles of sanitation and hygiene into all races with equal success.

The T.A.B. vaccine is made from cultures of *B. typhosus* and paratyphoid bacilli A. and B., but my mixed vaccine consists of the above-mentioned bacilli with the paratyphoid bacillus C. in addition. The C. bacillus gives rise to paratyphoid fever all over the world, and for that reason I include it in my mixed vaccine. The bacilli are grown on agar for twenty-four hours at 37° C., emulsified in normal saline, and the bacterial suspension is then heated in a water-bath at about 55° C. for one hour. It is essential to employ as low a temperature as possible for the preparation of the vaccine. I always emulsify the bacilli in saline containing 0·1 per cent. formalin, so as to avoid heating the microbes, and have found this method to be efficient.

The vaccines are in use for six months, and should be stored in a cool cupboard in the dark. The inoculations should be given subcutaneously, and preferably in the afternoon or evening. The same area of tissue should not be used for subsequent injections, and it is well to avoid an area with prominent veins, as thrombosis may complicate the local tissue reaction. The amount of local and general reaction which occurs at the present day is usually not severe, but considerable local and general reaction may occur. If 10 grains of aspirin are taken with

hot tea within six hours of the inoculation a general reaction will probably be prevented. It is a good plan to advise those who have not been inoculated previously to avoid using the arm or part of the body in which the inoculation has been given, except for the necessities of life, until the local reaction has disappeared. No alcohol should be taken for the twenty-four hours following the inoculation, extremes of temperature should be avoided, and it is advisable to take a purgative on the night of the injection. It may be considered that such precautions are unnecessary, but from experience I advise these measures to be adopted whenever possible.

Dosage.—The pure typhoid vaccine is seldom required at the present day, so the dosage of the mixed vaccine is given as follows :—

B. typhosus	. .	1,000,000,000 bacilli.
B. para B.	. .	750,000,000 ,,
B. para A.	. .	750,000,000 ,,
B. para C.	. .	750,000,000 ,,

This total quantity is represented in 1 c.c. For adults I give 0·5 c.c. for the first dose, and seven to ten days later 1 c.c. Some authorities employ a third and even a fourth dose of 1 c.c. at the same intervals as between the first and second doses, but I have never adopted this procedure. For children the maximum dose should be the same as for adults if the inoculations can be given in doses of 0·25, 0·5, 0·75, and 1 c.c. at weekly intervals. If children under ten have to be inoculated it is well to reduce the maximum dose to one-half the adult dose and subdivide the dosage as far as possible.

It is well to avoid inoculating T.A.B.C. vaccine if pyrexia of 100° F. or over is present, in cases of active pulmonary tuberculosis, during acute infections, or in the early stages of typhoid or paratyphoid fevers.

Revaccination should be employed for those who are liable to be exposed to infection every two or three years.

In the preparation of the typhoid vaccine some observers employ more than one strain of *B. typhosus*, because of certain slight serological differences which are claimed to exist among strains of this bacillus. I employ one strain only of *B. typhosus*, which has been proved to have full immunising properties.

Cholera

This vaccine is usually made from cultures of the true spirillum of Asiatic cholera grown on agar for twenty-four hours, washed off with saline, and killed by exposure to a temperature of 58° C. to 60° C. for one hour. If found to be sterile, the bacterial emulsion is diluted with carbolised (0·25 per cent.) saline. The cholera vaccines which I prepared and used in the East on a large scale during the Great War were killed with formalin (0·1 per cent.).

The dosage differs according to various authorities, as some use 1,000 and 2,000 million vibrios for the first and second doses respectively; others employ 4,000 and 8,000 millions. I give 2,000 million vibrios, which amounts to 0·5 c.c. for the first dose, and 4,000 millions (1 c.c.) for the second dose at an interval of seven to ten days.

The local and general reactions following prophylactic inoculation with cholera vaccine prepared with formalin (0·1 per cent.) and injected in doses of 2,000 and 4,000 millions are seldom severe in my experience.

Revaccination must be employed at much more frequent intervals than in the case of T.A.B.C. vaccine. The usual period is about every three to six months. Some authorities recommend that cholera vaccine should be included with T.A.B.C. Personally, I think it is better not to

increase the bulk of the vaccine, but to inject cholera vaccine into a separate tissue area and at a different date.

Plague

This vaccine is prepared from cultures of *B. pestis*. Haffkine's vaccine is made by growing *B. pestis* at 25° to 30° C. for from five to six weeks in broth flasks to which sterile olive oil is added so as to act as a float for the surface growth of the bacillus. The whole contents are then well mixed and sterilised at 65° C. for from one to three hours; 0·5 per cent. phenol is then added as a preservative. The dose is 3 c.c. subcutaneously, repeated in eight to ten days. Protection lasts about three months, but does not appear until some days after the inoculation.

Kolle used forty-eight hours agar growths emulsified in saline and sterilised at 70° C. for one hour, although 60° C. is sufficient for the purpose. The vaccine should contain one of the usual preservatives. Hans Zinsser recommends saline suspension of agar cultures grown for twenty-four hours, and then heated for one hour at 65° C.

Saline emulsions of agar growths can be sterilised with formalin, as in the case of other vaccines. The dosage of vaccines prepared in this way is 1,000 millions, followed by a second dose of 2,000 millions in ten days. In my experience, the local reaction following the inoculation of the vaccine may be very considerable, although usually insignificant, but it is especially likely to be severe if the dosage is much beyond 2,000 millions.

Influenza

The great majority of human beings are susceptible to influenza, which is one of the most serious of all epidemic diseases. It is therefore advisable not to place too much reliance on the belief that one possesses a natural immunity,

but the converse, that some individuals are hypersusceptible and apparently develop no immunity, even after two or three attacks, appears to be correct. Whether we hold that influenza is due to a filter passer or to the influenza bacillus does not influence the fact that the complications of this disease are of so much importance that they must be prevented if possible. The chief microbes responsible for these complications are pneumococci, streptococci (hæmolytic and non-hæmolytic), *B. influenzæ*, *S. aureus*, and to a less extent, *B. friedlander*, *B. septus* and *M. catarrhalis*. No one will deny the importance of these microbes in the causation of the various complications, more especially those of the pulmonary system, but considerable arguments—as yet unsettled—range round the primary ætiological factor. A long list of bacteria which may produce the important complications has been given above, and it is suggested that the *B. pneumosintes* of Olitsky and Gates or *B. influenzæ* is the essential microbe of the disease. Mixed vaccines of some of the above mentioned microbes, except *B. pneumosintes*, are widely used, while some workers employ a pure vaccine of the influenza bacillus, and of late an attempt has been made to prepare a *B. pneumosintes* vaccine, but of this I have had no experience.

The following is the composition of a mixed vaccine I employ :

The Mixed Vaccine

B. influenzæ . . .	800	million	per c.c.
Hæmolytic streptococci .	800	,,	,,
Non-hæmolytic streptococci	800	,,	,,
Pneumococci I. and II. .	800	,,	,,
S. aureus . . .	1,000	,,	,,

The dosage is 0·25 c.c. ; seven to ten days later 0·5 c.c. ; and at a similar interval 1 c.c.

The mixed vaccines may include *M. catarrhalis* at 600 millions per cubic centimetre.

The local and general reactions are usually mild. The conclusions which I have come to from my own personal experience among the population I have inoculated are as follows :—

1. The vaccine should be given more especially with the idea of preventing the pulmonary complications.

2. The duration of the immunity is short, for after a period of three to four months there may be complete absence of protection.

3. Among vaccinated cases complications are of less severity.

The obvious criticism is that these conclusions are mere expressions of opinion as opposed to statistical records, but they have the advantage of being direct personal experience.

The Common Cold

Many people in this country have two attacks of the common cold each year, some have three or more attacks, and cases occur where one attack immediately follows upon another. The loss of efficiency is considerable, to say nothing of the inconvenience and unpleasantness experienced, while not infrequently sinus infections may develop. As regards the ætiology, here again there are two schools : (1) The filter passer ; (2) similar microbes to those found in the complications of influenza.

The microbes which are found most frequently in my experience are pneumococci and *M. catarrhalis*. Patients can be protected against common colds by stock vaccines, such as are recommended for influenza, or cultures can be made at the height of the disease, and autogenous vaccines prepared. I know of many instances when *pure* cultures of pneumococci have been obtained from the fauces during

the height of the common cold, and again during subsequent attacks. The vaccine should be given at weekly intervals and in increasing doses, commencing with about 50 millions of pneumococci, and of the other bacteria referred to in similar proportions, after the acute illness has completely subsided. If a vaccine is to be employed as a precautionary measure at a period when the individual has been free from evidence of infection for a considerable period, then larger doses of vaccine can be given as recommended for the prevention of influenza.

Whooping Cough

Vaccines prepared from the bacillus of Bordet and Gengou are used for preventative inoculation. Three or more subcutaneous injections are given at weekly intervals, commencing as soon as possible after exposure to infection.

The dosage for children is about 500 million, and two or more doses of 1,000 million, according to the child's age and state of health, while for adults 1,000, 2,000 and 4,000 million can be given at intervals of about a week.

Pneumonia

Attempts to produce immunity to lobar pneumonia have been made of recent years by means of vaccines of the pneumococcus. Almroth Wright introduced this method of immunisation for the natives of the Rand, and Lister in South Africa has employed immunisation on a large scale with a polyvalent typed pneumococcal vaccine. Saline suspensions of typed pneumococci grown in suitable media are employed. Glucose broth, serum broth, serum agar, Dorset's egg medium, and blood serum are used by various workers to obtain abundant growths, and the cultures are killed by heat or chemicals. The chief

difficulty is to obtain sufficient growth of the microbes, as large doses are required for immunisation.

The vaccine should be polyvalent and prepared from strains of pneumococci, types I., II. and III. As regards type IV., the difficulty is due to the number of pneumococci included in this group, although an attempt has been made to meet with this difficulty by employing several of the type IV. strains. The dose of the pneumococcal vaccine is, therefore, considerable. The first injection should contain 4,000 millions or more of the mixed types in 0·5 c.c., and the second and third doses 8,000 millions or more in 1 c.c. The injections are given subcutaneously. It is now generally agreed that protective inoculation against pneumonia is necessary for those who are known to be susceptible, and for individuals who are massed together in a locality, more especially if an epidemic of pneumonia has occurred. Lister's results in South Africa certainly warrant a full trial with this form of immunisation.

Tuberculosis

Vaccination of New-born Infants with "B.C.G." Vaccine.

Calmette [1] has recently introduced a method of immunising children against tuberculosis. He cultivates the bacillus in an artificial medium of alkaline beef bile, rich in lipoids, which produces an abundant growth of low virulence. Two hundred and thirty successive subcultures grown at 38° C. over a period of thirteen years have resulted in the growth of a bacillus which is avirulent for animals, and it has not been found possible to restore its virulence, even when inoculated or injected in doses of 100 mgms.

[1] Calmette, A., Guérin, C., Nègre, L., and Boquet, A. (1926): "Prémunition des nouveau-nès contre la tuberculose par le vaccin B.C.G.," *Revues de la Tuberculose*, 3 ser., T. vii., I., 5–53.

Large quantities can be injected, or taken by the mouth, without exciting a tuberculous process, as proved at the post-mortem examinations on experimental animals. This vaccine is known as B.C.G. (*Bacillus Calmette-Guérin*).

The protection lasts over a year, and the vaccination can be repeated yearly by fresh ingestion without ill-effect. Tuberculin tests should not be used in cases previously vaccinated with B.C.G. The first child was vaccinated with B.C.G. in July, 1921, at the Charitée Hospital, Paris, and since then 5,183 cases have been vaccinated without ill-effect. Of this number, 1,317 have been vaccinated for more than twelve months, and of these 586 were brought up by mothers suffering from active tuberculosis ; among these latter there were only eleven deaths, or 1·8 per cent., from tuberculosis. The total number of deaths among the 1,317 cases vaccinated for twelve months was 107, which gives a mortality of 7·9 per cent., of which only 0·7 per cent. were due to tuberculosis. The findings of Calmette and his co-workers show that 24 per cent. of unvaccinated children whose mothers have active tuberculosis die within the first year of life. Calmette considers that preventative vaccination with vaccine B.C.G. does not produce an immediate immunity, and that two or three weeks must elapse before complete immunity is produced. During this period every effort should be made to avoid infection. This form of vaccination should be carried out at birth. It possibly lasts about three years, but a trial should be given to repeated vaccination at the end of the first and third year.

The vaccine must always be freshly prepared, and cannot be kept for more than ten days. It should be used for new-born infants or within the first ten days of life,

except for revaccination, as already referred to. It is supplied by the Pasteur Institute, and is given in three doses at twenty-four hours' intervals in a spoon with milk at body temperature, half an hour before a meal.

Rabies

It is open to criticism to include rabies and smallpox among the diseases to be prevented by bacterial vaccines. For various reasons, however, it was decided that it would be an advantage to include them in this series.

The preventative treatment for rabies was introduced through the genius of Pasteur. On Monday, July 6th, 1885, a little Alsatian boy, Joseph Meister, was the first human subject to be inoculated against rabies. He had been brought to Paris to see Pasteur, suffering from multiple bites of two days' duration. As Pasteur was unable to cultivate the microbe of rabies on artificial media, he employed the infected spinal cords of rabid rabbits for the preparation of the vaccine.

This vaccine is now employed throughout the world, but with very little alteration in the method of preparation from that originally introduced by Pasteur. Whatever form of vaccine is employed, the injections are given subcutaneously, and I always employ the flank, using right and left on alternate days. It is well to inject into a fresh area of tissue on each occasion. Patients should avoid active exercise and alcohol, except in *very small* quantities, during the period of treatment and for a week after its completion.

No ill-effect occurs during the first week, but on and after the seventh and eighth injection large tender œdematous areas may appear, which cause considerable skin irritation and inconvenience to patients. Two or three days' rest will generally allow the swellings to subside,

especially if an evaporating lead lotion is applied while they are at their height. The injections are given daily for fifteen days for ordinary cases, but patients who have had multiple bites are inoculated for eighteen days, and those who have been bitten on the head and neck receive daily injections for twenty-one days. If the treatment has been much delayed, or if the bites are on the head or neck, or are multiple, it may be as well to give two inoculations each day for the first two or three days. The Pasteur treatment consists of taking small fragments of the spinal cords of rabid rabbits (5 mm. long), which have been dried for so many days and are then preserved in glycerine. At the commencement of treatment cords which have been dried for six days are employed, but in course of time rabid cords which have been dried for only two days are injected. The fragments of spinal cord are emulsified in saline, and are then used for the inoculations. The vaccine employed for preventative treatment for rabies, therefore, contains the spinal cord of the rabid animal together with the microbe, from which it cannot be separated for purposes of this kind.

The method of inoculation is as follows :—

Day of Injection.		Dried for.	Amount to be Injected.	
1st day	Rabid rabbit cord	6 days	3 c.c.	
2nd ,,	,, ,,	6 ,,	,,	
3rd ,,	,, ,,	5 ,,	,,	
4th ,,	,, ,,	4 ,,	,,	
5th ,,	,, ,,	3 ,,	,,	
6th ,,	,, ,,	5 ,,	,,	
7th ,,	,, ,,	4 ,,	,,	
8th ,,	,, ,,	5 ,,	,,	
9th ,,	,, ,,	4 ,,	,,	
10th ,,	,, ,,	3 ,,	,,	
11th ,,	,, ,,	2 ,,	,,	
12th ,,	,, ,,	5 ,,	,,	
13th ,,	,, ,,	4 ,,	,,	
14th ,,	,, ,,	3 ,,	,,	
15th ,,	,, ,,	2 ,,	,,	Ordinary cases.
16th ,,	,, ,,	4 ,,	,,	
17th ,,	,, ,,	3 ,,	,,	
18th ,,	,, ,,	2 ,,	,,	Cases with multiple bites.
19th ,,	,, ,,	3 ,,	,,	
20th ,,	,, ,,	2 ,,	,,	
21st ,,	,, ,,	2 ,,	,,	Head and neck cases.

Many modifications have been introduced so as to obtain the emulsions ready for use without any preliminary treatment.

Carbolised antirabic vaccines can be prepared by making a 4 per cent. emulsion of the brain, medulla, and spinal cords of rabbits which have died from rabies after inoculation with the "fixed" rabies virus (virus of constant strength obtained by passage through rabbits), in sterile normal saline containing 0·5 per cent. phenol. The carbolised vaccine is put up in the ordinary vaccine bottles.

This vaccine, if kept in a dark and cool place, retains its value for three months at least. The bottle is well shaken and an ordinary 2-c.c. syringe is employed for the inoculations.

The dosage for adults is 2 c.c. daily for ordinary cases, but for those who have had multiple bites, or when the treatment has been delayed, or the bites have been on the head and neck, the amount injected can be increased up to 4 c.c. Large injections (4 c.c.) should, however, be employed for a few days only.

Smallpox

The preventative treatment for smallpox, like rabies, is by inoculation with material containing the virus from which it cannot be separated for purposes of immunisation. The description of smallpox vaccination is only such as will illustrate the differences from bacterial vaccination.

Vaccination against smallpox obtained by inoculating the material from the pustule of a smallpox patient into a healthy person in order to produce a mild attack of the disease and so establish immunity is said to have been practised in China about the year 1000 B.C. It was largely

due to Lady Mary Wortley Montagu, wife of the British Ambassador in Constantinople, that this form of vaccination, which was widely practised by the Turks, was introduced into Great Britain in 1718. Unfortunately, smallpox transmitted by this means was sometimes of a severe type, which terminated fatally.

We now come to what is known as Jennerian vaccination. It was a belief among farmers and farm workers that those who had sores on their hands, contracted from similar lesions on the teats of cows, escaped true smallpox.

Edward Jenner, on May 14th, 1796, vaccinated a boy, James Phipps, with the material from a cow pock on the hand of a dairymaid, and on July 1st of the same year he inoculated this boy with the material from a pustule from a genuine case of smallpox without producing the disease. In 1798 he inoculated a child direct from a vesicle on the teat of a cow, and then transferred the infection from arm to arm in five other children. These children were then inoculated with smallpox "virus" without ill-effect. These observations furnished the proof that cowpox affords protection against smallpox.

Both forms of active immunisation were, therefore, carried out with infected tissues and body fluids from which the virus could not be separated.

It is not possible to discuss further the interesting observations which have been made on the relationship of cowpox and smallpox.

Preparation of Cowpox Vaccine.—Healthy female calves, two to four months of age, are usually employed for the preparation of the vaccine. They should be passed free of tuberculosis. The skin of the belly, inner side of thighs, and flanks, is shaved and suitably prepared as in any other strict surgical procedure.

About 100 small scarifications are made into the pre-

pared skin, which are then sponged dry, and rubbed with the virus. The lesions are then dried and covered with sterile gauze, and the animals are kept clean under strict supervision. The virus used for the calves is obtained from the arms of vaccinated children. This human virus is inoculated into the skin of the abdominal wall of the calf, the lymph from the vesicles which form is glycerinated, tested on rabbits, and finally used for inoculation of calves as referred to above.

As a rule, in about five to six days the vaccine vesicles on the calf are developed, so that the material can be collected. The calf is killed and placed on an operating table and the technique which is employed during the collection of the vaccine lymph is the same as in the strict surgical technique employed in an operating theatre. The whole of the fluid and solid portions of the vaccine are removed by means of a curette and collected in a sterile vessel and mixed with four times its weight of glycerin and water (50 per cent. glycerin, 1 per cent. phenol, 49 per cent. of water). The mixture is kept for three or four weeks to reduce the bacterial activity, then ground, passed through a sieve and put up in small capillary tubes, which are sealed and remain active for three months if kept in a *cool*, dark place.

When the vaccine has been examined and proved bacteriologically to be ready for use, it must then be proved efficient by the inoculation of the human subject.

The Technique of Vaccination.—The essential factor in vaccination is the introduction of the virus through the epidermis, and absorption by the lymphatics and blood vessels of the corium.

The usual site is the upper arm on the outer side, near the insertion of the deltoid tendon.

The skin should be carefully cleansed and dried ; a

drop of the glycerinated virus is put on the arm and the skin scratched with a sterile needle. The skin scratches should not draw blood. After the skin has been scratched longitudinally the vaccine lymph is rubbed into the abrasions with the needle. The vaccinated area is allowed to dry, and then covered with a sterile dressing.

One inoculation of the vaccine lymph is sufficient, but, if necessary, two or more inoculations are made at the same time to ensure success and more rapid immunisation.

Care must be taken to keep the vaccinated area clean and avoid bacterial contamination.

A slight redness immediately follows vaccination, and subsides rapidly. About the third day a red elevation appears ; about the sixth or seventh day an umbilicated vesicle appears, filled with serum and surrounded by a red area. By the tenth day the lesion is at its height, showing a red area with several minute vesicles on the surface. Subsequently the lesion diminishes.

Vaccination produces efficient, long-standing immunisation, but probably revaccination should be carried out every seven years and during smallpox epidemics.

CHAPTER V

ON VACCINE THERAPY IN ACUTE GENERALISED BACTERIAL INFECTIONS

EVER since bacterial vaccines have been employed in the treatment of infective processes in man the question has been discussed as to whether such vaccines are indicated in acute generalised infections. I have weighed the arguments for and against vaccine therapy with all possible care, and have considered the results which I have obtained in various generalised infections treated with stock and autogenous vaccines, sensitised and otherwise, with the result that I am directly opposed to vaccine therapy in the acute stages of generalised infections. Bacterial vaccines have been employed from time to time for the treatment of streptococcal septicæmia, pneumonia, and typhoid fever, to quote a few examples of generalised infections. In acute streptococcal septicæmia there is no proof that an injection of an autogenous or stock vaccine has any therapeutic value.

Those who employ bacterial vaccines for the treatment of acute lobar pneumonia do so chiefly with the idea of accelerating the onset of the crisis, and therefore recommend that vaccines should be employed at the earliest possible period of the disease. It is obvious that a stock vaccine only is available at the outset, but, as it should belong to the same type as the infecting microbe, some delay must occur. It is difficult to appreciate how the administration of a bacterial vaccine in an acute disease of such short duration as acute lobar pneumonia can assist in the production of immunity, and in my own

experience vaccine treatment has failed to produce any beneficial effect. In the literature with which I am acquainted there is nothing to support the use of specific vaccines, in spite of the fact that one enthusiast recommends the injection of his vaccine daily until the temperature reaches normal !

Wiltshire,[1] in a paper with MacGillycuddy, claimed good results in the treatment of fifty cases of typhoid fever with stock typhoid vaccine. These authors regarded typhoid vaccine as a most valuable therapeutic agent, and recommended that it should be given at the earliest possible period of the disease. They employed an initial dose of 250 millions, and an interval of three days between the subsequent injections. I consider the dosage excessive, and the interval of three days is too short for therapeutic purposes in an acute infective disease ; but these authors were very satisfied with the results which they obtained.

Gay [2] has reviewed the results of the treatment of typhoid fever with typhoid vaccines, which are summarised in the accompanying table :—

THE TREATMENT OF TYPHOID FEVER BY VACCINES (1913–1917) (GAY)

	Observers.	Total cases.	Estimates based on.	Benefited, per cent.	Mortality per cent.
Untreated vaccine subcutaneously	30	1,001	512	46	14·5
Sensitised vaccine subcutaneously	14	593	239	69	8·0
Untreated vaccine intravenously	22	501	233	62	13·0
Sensitised vaccine intravenously .	12	487	316	85	11·0

[1] Wiltshire, H. W., and MacGillycuddy, A. R. N. (1915) : " Experience in the Treatment of Typhoid Fever by Stock Typhoid Vaccine," *Lancet*, September 25th.

[2] Gay, E. P. (1918) : " Typhoid Fever considered as a Problem of Scientific Medicine." The Macmillan Co., New York.

There is no strong evidence, in my opinion, in favour of vaccine treatment with ordinary or sensitised vaccines, administered subcutaneously or intravenously, as judged by these records collected by Gay, and there was no appreciable effect on the frequency of relapses.

Acute bacterial infections in man can be divided into three main groups : (1) When the infective process is so rapidly localised that recovery takes place. (2) Those cases in which rapid dissemination occurs by the blood stream and lymphatics, so that the defensive powers of the tissues are completely overwhelmed. (3) The cases which occupy an intermediate position between groups (1) and (2), in which the infection shows a tendency to become localised but, at the same time, bacterial dissemination occurs to a limited degree.

In the first group vaccine treatment may be necessary when the infective process has become localised and, yet, recovery is delayed. There is no indication whatever for vaccine therapy for cases included in group (2). There is a wide difference of opinion as regards the cases included in the third group. I consider that no advantage will occur from vaccine therapy until the clinical condition conforms to that referred to in group (1) ; while it is well to realise that although all border-line cases must be considered on their own merits, without restrictions by hard-and-fast rules, yet injudicious treatment may rapidly produce a fatal result.

There is no question that so-called " surgical treatment " in the early stages of some of the acute infective processes, at a time when Nature is attempting to localise the process, has resulted in dissemination of the infection, and a fatal result has occurred. Fatal results have also followed injudicious vaccine treatment.

It is common knowledge that the evacuation of pus is

essential to relieve tissue tension, to increase tissue activity, to allow the circulation of the body fluids, and for the removal of toxic products. We also know that fomentations and other hot applications assist in tissue repair. On the other hand, incisions into inflamed tissues in patients suffering from acute bacterial infections when pus has not actually formed *may* lead to tissue necrosis and dissemination of the infecting microbes and seriously prejudice the patient's chances of recovery.

Unfortunately, our knowledge of the part played by the tissue cells in acute bacterial infections is much less understood than that of the body fluids; but until this knowledge is forthcoming serious errors will be perpetrated during the treatment of acute bacterial infections.

Hans Zinsser,[1] who discusses in detail the treatment of acute generalised infections with bacterial vaccines, sums up this question as follows: "In generalised systemic infections we must sharply distinguish between cases of acute sepsis, in which the bacteria are actively growing and multiplying in the circulation, and other cases in which blood cultures are positive only because the bacteria are being constantly discharged into the circulation from a focus in the tissues. In the former the defences of the body are overwhelmed by an extensive flooding with the bacteria, and vaccines, if not harmful, are at any rate utterly useless, since the antigen is already so extensively distributed throughout the tissues that, if the body were capable of responding with sufficient antibody formation, this would unquestionably occur without the small additional amount furnished in the bacterial emulsion. Vaccination in such cases is entirely

[1] Zinsser, Hans (1923): "Infection and Resistance," 3rd edition. The Macmillan Co., New York.

analogous to an attempt to stimulate a degenerated heart muscle with strychnine." Further, he states that "In acute diseases which run a definite course—typhoid fever, pneumonia, dysentery, cholera, plague, and a number of other conditions—vaccine treatment during the course of the disease has not much theoretical justification. In acute infectious diseases any effect that has been claimed for vaccines, we believe, has been due to the non-specific reactions . . . and in no sense to a specific immunising effect of the injected bacteria."

It may be mentioned here that Gay considers the advantages claimed for the treatment of typhoid fever with typhoid vaccine are due to a non-specific action.

When sensitised vaccines were introduced by Besredka, it was believed by some workers on this subject that a remedy had been obtained for some of the acute bacterial infections, but again in my own experience the results are no better than with ordinary vaccines.

At one time it was believed that success would follow if vaccine therapy was employed in the treatment of malignant endocarditis, but the treatment of these cases with stock and autogenous vaccines, sensitised and ordinary, has led me to the conclusion that vaccine therapy is useless in controlling the temperature or in preventing the progress of the disease, and such cases as I have seen treated by others have helped to strengthen this opinion.

Although very occasionally I have seen a remarkable improvement, in a case of acute generalised infection, from one or more injections of vaccine, yet from wide personal experience I am opposed to vaccine therapy for cases of this kind.

CHAPTER VI

INFECTIONS OF THE GENITO-URINARY SYSTEM

Examination of Urine

In the case of the male sex, the urine can be passed direct into a sterile glass receptacle after cleansing of the meatus and surrounding tissues. In women and female children a catheter specimen of the urine should be obtained, unless special circumstances direct otherwise, and then the sample must be collected with all possible care. The fresh samples of urine, collected in sterile glass bottles, should be fully examined and cultures made. If there is any possibility of a unilateral infection of the kidneys, the samples of urine should be collected by catheterisation of the ureters.

Bacillus Coli Infections

Acute and chronic inflammation of the urinary tract due to *B. coli* is one of the commonest infections to which the human body is liable, and the amount of ill-health caused in men, women, and children by these infections is a much more serious question than is usually recognised. *B. coli* infections of the urinary tract occur in children and adults of all ages, but most commonly in (1) young children, especially females; (2) in women, during pregnancy and after confinement; (3) subsequent to acute illnesses; (4) among patients with obstruction to the flow of urine, resulting from such conditions as enlargement of the prostate gland; (5) in cases of chronic constipation and diarrhœa, especially in women. From

these remarks the frequency and importance of these infections will be realised. It is now known that the persistence of infection after the acute stage is over is a most serious problem, more especially as treatment is most unsatisfactory in chronic cases. *B. coli* infections occur as bacilluria, bacilluria with hæmaturia, pyuria, and pyuria with hæmaturia.

Dudgeon, Bawtree and Wordley [1] have shown that two main groups of colon bacilli occur in these cases: (1) hæmolytic and (2) non-hæmolytic. Infections caused by hæmolytic bacilli are commoner in the male sex, while in the female the converse is true, although the hæmolytic colon bacillus occurs more frequently in women suffering from acute coli fever.

The division of colon bacilli into hæmolytic and non-hæmolytic groups, and the further sub-grouping with anti-sera by Dudgeon and his co-workers, has rendered possible the identification of a colon bacillus isolated from the urinary tract at one period of a patient's illness with that obtained at a later date. In my experience it is the usual practice to find the same organism on each occasion, even after an apparent cure is effected, should a further attack of coli fever develop. It is very uncommon for another strain of colon bacillus to be obtained under these circumstances. It is also uncommon to find a double infection with colon bacilli, or, in other words, two different strains present at the same time. These facts are important in the treatment of these infections, whether by surgical or bacteriological methods.

Dudgeon and his co-workers endeavoured to ascertain whether stock colon vaccines could be employed rather

[1] Dudgeon, L. S., Wordley, E., Bawtree, F. (October 19th, 1921, and December 7th, 1922): "On *B. coli* Infections of the Urinary Tract, especially in Relation to Hæmolytic Organisms," *Journ. of Hygiene*, vol. xx., No. 2; vol. xxi., No. 2.

than autogenous. It was found that hæmolytic colon bacilli could be readily grouped by the preparation of a few anti-sera, but with the non-hæmolytic strains it was an entirely different matter. Some strains of non-hæmolytic colon bacilli were found to produce an autogenous anti-serum only ; in other instances a satisfactory anti-serum could not be produced by any method at our disposal.

If we hold the view that treatment by vaccines depends upon specific proteins rather than on any foreign protein substance, then, for the reasons already mentioned, it is essential to employ autogenous vaccines for all cases of infection caused by non-hæmolytic bacilli ; but stock vaccines can be employed for *B. coli* infections caused by hæmolytic strains after they have been grouped with our anti-sera. Dudgeon and his co-workers have shown, and Herrold [1] has confirmed their results, that the source of these hæmolytic colon bacilli may be from the intestinal tract. My observations on the immunisation of patients suffering from *B. coli* infections with autogenous vaccines has led me to believe that a high degree of immunity, as measured by the presence of immune substances in the blood, is seldom found, and that, as a rule, these immune substances are only present in the blood in low titre before the commencement of vaccine treatment. There is a possibility that the very deficient formation of immune substances may help to explain the frequency of relapses, and also the difficulty in effecting a cure among patients suffering from *B. coli* infections of the urinary tract.

Treatment with *B. coli* vaccines is employed (1) For

[1] Herrold, R. S. (1922) : "The Relation of the Colon Bacilli of Renal Infections to Strains from other Sources, and Observations on the Hæmolytic Colon Bacilli," *Journ. of Urology*, vol. vii.

prophylaxis ; (2) therapeutically. I have used vaccines prepared in the manner already referred to, and also sensitised dead bacilli, but have never obtained success by the latter method when the former had failed.

Prophylaxis

For many years it has been considered a wise policy to attempt to immunise patients suffering from a *B. coli* infection of the urinary tract before a major operation is performed on the genito-urinary organs. This prophylactic treatment is, therefore, an entirely different problem from the immunisation of a *healthy* population to prevent infection. An autogenous vaccine should be employed, or a vaccine made from a colon bacillus of the same group. I have now employed preventative treatment previous to operation on a large number of cases. When time has permitted, three injections of a vaccine have been given, in doses of 100, 500 and 1,000 million, at intervals of one week. If no ill-effects occur from 100 million bacilli, it is then safe to employ the full course of prophylactic inoculation ; but if there is obstruction to the outflow of urine, acute symptoms of coli fever will probably occur.

The colon bacillus is especially liable to give rise to an attack of acute coli fever if there is obstruction to the urinary outflow, and this is more especially liable to occur from congestion of the urinary passages produced during vaccine treatment. For these reasons it is unwise to give large doses of colon vaccines to patients with enlargement of the prostate and obstructed urinary outflow, unless the obstruction is relieved before the vaccine treatment is commenced. I have seen patients whose condition has been greatly aggravated during prophylactic inoculation owing to these facts not being sufficiently appreciated.

Patients suffering from frequency and slight pyrexia may develop a severe reaction from a large dose of *B. coli* vaccine, but, on the other hand, unless a dose of at least 100 million bacilli can be given, it is quite useless to attempt prophylactic inoculation. It will thus be apparent that cases for prophylactic inoculation must be carefully selected, or else much more harm than good will ensue, as we are not dealing with healthy subjects, and the ill-effects that may arise from this prophylactic treatment are of a serious nature.

Therapeutics

Before vaccine treatment is commenced the clinical condition of the patient should be fully considered. Those who have had a wide experience of *B. coli* infections of the urinary tract will probably agree that success, as shown by *complete cure*, following vaccine administration is uncommon.

In *pure bacilluria*, without urinary symptoms and no evidence of general toxæmia, vaccine treatment should not be undertaken, as it is useless. It would seem hardly necessary to urge this point, but experience has taught me that such cases are not infrequently treated by vaccines in the vain hope that a cure will be effected. If, however, a patient has sciatica, lumbago, joint pains, or other complication which is thought to be due to the bacillary infection, then a *B. coli* vaccine may be employed for the treatment of these symptoms.

Bacilluria and Pyuria.—Children with bacilluria and pyuria which have resisted the effects of the ordinary treatment employed in the acute stages of the disease, and in whom no exciting cause is found, may derive considerable benefit from treatment with autogenous vaccines. The symptoms may disappear rapidly and the urine return

to the normal state. I have seldom employed this treatment for babies or very young children, as the necessity does not arise, but in children over the age of five the dosage is slightly less than the average dose for adults, commencing with 20 million bacilli at intervals of one week, and increasing the dosage as circumstances permit. No hard-and-fast rule can be laid down, as each case has to be considered on its own merits, but doses of 20, 40, 100, 200, 300, 400 and 500 millions of an autogenous formalised *B. coli* vaccine, given at weekly intervals, will generally meet the case. If urinary symptoms return during treatment, then the dosage must be reduced accordingly. Any other treatment required should be continued during the course of vaccine therapy. It cannot be too strongly emphasised that when the desire for micturition occurs this act must be accomplished, as failure to do so may be the cause of an attack of acute coli fever.

In adults, the various symptoms associated with chronic pyuria and bacilluria may be rapidly relieved by vaccine treatment, so that a patient believes that a complete cure has been effected, but in reality the condition of the urine may not be much improved. I consider it is uncommon for the infection to disappear during, or as a result of, vaccine therapy, whatever dosage is employed or whatever method of preparing the vaccine is adopted. To obtain the best results with *B. coli* vaccines, treatment should be commenced at the earliest possible period *after the acute symptoms have subsided.* If during vaccine treatment the symptoms are aggravated, and we are satisfied that the dosage is correct for the individual case, then it is necessary before further use of vaccines is decided upon to catheterise the ureters in order to exclude a chronic suppurative process localised to one kidney.

B. coli vaccines should be prepared, as already stated, from autogenous strains, or from strains belonging to the same group; the former is the more satisfactory, and the dosage for adults varies according to the individual and the nature of the lesion. I usually commence with a dose of 25 million bacilli, and then increase the dosage gradually so as to avoid aggravation of the urinary symptoms.

I have been unable to obtain any advantage from massive doses of vaccines in cases of *B. coli* infections. At one time it was believed that what was impossible to accomplish with ordinary doses was possible with massive doses, a view which I consider from experience to be incorrect. Graduated doses of vaccine containing 25, 50, 100, 200, 400, 600, 800 and 1,000 million bacilli, according to circumstances, with a maximum dosage which should not exceed 2,000 millions, are, on the average, correct. The injections should be given subcutaneously, employing a fresh area of tissue on each occasion. The larger doses may cause redness of skin, local tenderness, and slight rise of temperature. If a patient develops a definite reaction in the urinary passages at the outset, it is well to increase the dosage more gradually and to prolong the interval between the injections. All other necessary treatment should be carried out at the same time as with any other therapeutic measure.

Acute Cases of B. coli *Fever.*—The alkaline treatment should be commenced at the earliest possible moment. Vaccine therapy is liable to aggravate the symptoms, unless employed with considerable care; the vaccine should be given in doses of 20 millions to commence with, after the patient's temperature has been afebrile for about two days. It is useless to attempt to treat the

febrile stages of the disease by vaccine therapy, whether sensitised or ordinary vaccines are employed.

Special Group of Hæmolytic Bacilli.[1]—In 1924 I drew attention to cases of acute infection of the urinary tract due to bacilli in many respects resembling *B. coli*, but which formed permanent blue colonies on litmus lactose agar, slowly fermented lactose broth, did not ferment cane sugar, but fermented mannite, dulcite, dextrose and maltose, formed indol, clotted milk, and lysed red blood cells. Bacilli with these reactions were readily grouped with one anti-serum. A very large number of cases have now been met with, due to bacilli with similar cultural and serological reactions, as described above; but as certain cultural and serological differences have been found among such bacilli, further sub-grouping has been necessary. The majority of the strains, however, belong to the main group.

Every infection caused by the above-mentioned hæmolytic slow lactose-fermenting bacilli has run a very acute course, infinitely more severe than usually occurs in true coli fever. The temperature has persisted longer, and the general feeling of ill-health has been infinitely more severe than the urinary symptoms, so that a diagnosis of typhoid or paratyphoid fever has been made at the outset in some cases. In fact, it is surprising how often the diagnosis of these cases is at fault. These patients are hypersensitive to autogenous vaccines prepared in the usual way, if employed in the acute stages of the disease before the temperature has subsided. Vaccine treatment must not be commenced until the temperature has been normal for about five days or more;

[1] Dudgeon, L. S. (March 21st, 1924): "Acute Infection of the Urinary Tract due to a Special Group of Hæmolytic Bacilli," *Journ. of Hygiene*, vol. xxii., No. 3.

during this period the alkaline treatment should be enforced, otherwise an acute exacerbation of the symptoms will occur. It must be understood that a reliable bacteriological examination of the urine at the onset of the illness is essential. The dose of the vaccine at the outset is about 25 millions ; it is given in increased doses at weekly intervals, until doses of 500 to 600 millions are employed. Vaccine treatment must be discontinued if at any time during the treatment pyrexia should return, and should not be renewed until the temperature has remained normal for a few days. In the majority of instances patients infected with this type of bacillus are cured and the urine becomes sterile. This is an important point and very different from the history of true *B. coli* infections.

B. coli anærogenes.—Occasionally cases of acute and chronic infection of the urinary tract due to bacilli belonging to the so-called anærogenes group occur. Vaccine treatment is carried out on the same lines as in *B. coli* infections, and not infrequently with satisfactory results in my experience.

B. proteus.—The proteus bacillus gives rise to acute and chronic infections of the urinary tract, which may be accompanied by acute suppurative lesions. This organism can be isolated from the blood stream in the acute cases, and may be present in pure culture in the urine in cases of pyuria.

The not uncommon opinion expressed that *B. proteus* is a mere secondary invader is incorrect, as some of the most severe cases of acute urinary fever are primarily due to this organism.

In acute proteus infections, if vaccine treatment is employed, it must be carried out with infinite care as regards dosage and the intervals between the doses, otherwise aggravation of symptoms will ensue. It is

best to give 20 million bacilli to commence with, and to increase the doses very gradually until the febrile period is over, but in no circumstances should vaccine treatment be given unless there is a free flow of urine. The injections are to be given at weekly intervals and the doses varied according to circumstances, but 20, 40, 100, 200, 400, 600, 800 and 1,000 millions will usually meet the case. On the whole I prefer to wait until the acute symptoms have subsided before commencing vaccine treatment.

In chronic cases the first dose is 25 to 50 millions, and the dosage can be increased on a liberal basis, as *B. proteus* infections usually respond well to vaccine treatment.

The urine of patients showing the presence of *B. proteus* together with pus should be very carefully examined before vaccine treatment is commenced, as the few cases which have come to my notice with a communication between the bladder and the intestinal tract due to a malignant growth, and in one case to an inflammatory focus, have shown a proteus infection. In such cases, together with pus and bacilli, fragments of striped muscle and vegetable matter from the intestinal tract were found in the urine.

Streptococcal and Pneumococcal Infections

These infections, in my experience, are very uncommon, more especially pneumococcal, and although the cultivation of streptococci from urine is of frequent occurrence, it is usually of no moment. In some cases of pyuria due to *B. coli*, *B. proteus*, and *S. aureus* streptococci may also be present. When there is a streptococcal infection of the urinary tract, pus and streptococci are seen in film preparations of the urinary deposit, and the organism is readily cultivated from the pus, but, as already stated,

pure streptococcal infections are uncommon. My experience of vaccine treatment in such cases is very limited; those that have been treated have received 25 million streptococci at the outset, and then doses of 50, 100, 200, 400, 600 and 800 millions, given at weekly intervals. In cases of malignant endocarditis, streptococci may be present, sometimes in large numbers, in the urine, but vaccine treatment in these cases is useless. This subject, however, is more fully discussed under Malignant Endocarditis.

Staphylococcal Infections

S. aureus may occur in the urine in cases of septicæmia or pyæmia due to this coccus, or it may be the exciting cause of an infective process in the kidney, perirenal tissue, or bladder. *S. aureus* may be present in association with a calculus in the bladder, but the more common microbe in such cases is *S. albus*. Before vaccine treatment with *S. aureus* or *S. albus* is commenced it is necessary to exclude a calculus. When a local lesion due to either of these organisms has been proved, and there is no evidence of a primary cause which demands surgical treatment, then vaccine treatment should be employed on the same lines as in staphylococcal infections of the skin and subcutaneous tissues. At the commencement of treatment for adults a dose varying from 25 to 50 millions should be employed, and increased at weekly intervals. Vaccine treatment, however, in staphylococcal infections is seldom required.

Typhoid and Paratyphoid Infections

In the majority of cases vaccine treatment is not necessary, but in persistent bacilluria and pyuria, which *resist treatment with urotropin*, it may have to be con-

sidered. Such cases are, however, extremely uncommon, and from my own limited experience I would urge, before vaccine treatment be commenced, that an examination of the urinary tract is undertaken so as to exclude a unilateral septic nephritis, as vaccine treatment would be useless if such a condition was found. If vaccine treatment is required the dosage is the same as for *B. coli* vaccines.

Tuberculosis

In cases unsuitable for surgical treatment, or where, despite surgical intervention, tubercular foci remain, then tuberculin treatment should be tried. In all cases the patients must be at rest, the dosage must be very carefully regulated, and it is essential to commence treatment with very small doses of whatever preparation is preferred, *e.g.*, with T.R. it is best to commence with a dose of 0·00001 c.c. The injections should be given every five to seven days, but pain in the focal area, increased frequency of micturition, or hæmaturia must not be accentuated by the vaccine. The treatment will have to be continued for long periods, extending over many months. Unsatisfactory results will soon be apparent if there is any tendency to hurry the treatment. My own experience with tuberculin treatment has not been satisfactory, although I have tried T.R., B.E., and also bacillary emulsions made on the lines of ordinary vaccines. We must remember that cases of tuberculosis of the urinary tract which cannot be treated by surgical methods are in the advanced stages. There is no question that surgical treatment should be adopted whenever possible. Some observers claim good results in the treatment of tuberculosis of the male generative organs by means of tuberculin preparations, but I have had no personal experience of this mode of treatment.

CHAPTER VII

INFECTIONS OF THE GASTRO-INTESTINAL SYSTEM

MUCH time will be saved and endless discussion if it is realised at the outset that the presence of an organism in the fæces is not an indication of an intestinal infection with that organism. Vaccine therapy is so frequently employed for so-called intestinal infections without any intelligent understanding that it is necessary to consider this subject very carefully. Before a patient's fæces is examined bacteriologically and a vaccine prepared, various important questions arise. Firstly, what is the evidence that a patient is suffering from an intestinal infection due to a pathological process affecting the intestinal wall? Is there any evidence that such a process has once existed? The mere presence of abnormal bacteria in the fæces, or of the normal inhabitants in increased numbers, is not an indication for treatment with vaccines prepared from such organisms. Unfortunately the term "intestinal infection" has been so loosely employed, and so "readily proved," that it is without significance to those who have studied the bacteriology of the intestinal tract in man. It is especially in cases of unexplained anæmia and rheumatoid arthritis that mistakes most commonly occur. In the first place, it is necessary to have some acquaintance with the bacteriological findings[1] of the fæcal flora under varying circumstances: (1) The normal subject, (2) in

[1] Dudgeon, Leonard S. (1926): "A Study of the Intestinal Flora Under Normal and Abnormal Conditions," *Journ. of Hygiene*, vol. xxv., No. 2, July 26.

patients suffering from errors of diet, (3) in chronic constipation, (4) after active purgation, (5) in septic infections of the throat, respiratory, and urinary tracts, and (6) in infective processes of the intestinal walls. It is especially among " streptococci " which are employed so frequently for the preparation of intestinal vaccines that errors occur. From my own observations on the bacteriology of the fæces, I have found that all varieties of streptococci occur ; that the types of streptococci met with in normal fæces may exactly correspond with those found in the fæces in pathological processes of the intestinal tract ; that in infections of the throat and respiratory tract hæmolytic streptococci identical with the streptococci obtained from the throat and sputum may occur in the fæces in large numbers, that cases occur in which hæmolytic streptococci have been found to be abundant in the fæces, but have disappeared on alteration in the diet. Constipation may greatly increase the number of streptococci present in the fæces—in fact, in some cases of chronic constipation streptococci occur in enormous numbers ; on the other hand, in some cases of diarrhœa, a great increase is observed during the height of the trouble. Before this subject is more fully discussed it is advisable to refer briefly to the methods employed for the examination of the fæces.

Method of Examination

A bacteriological examination of the fæces is undertaken for the purpose of finding the presence of a microbe believed to be the cause of the patient's illness, or to ascertain whether a patient is an intestinal carrier of pathogenic organisms, or for the study of the fæcal flora with a view to the preparation of an intestinal vaccine, and it is this last question which concerns us at the

moment. Time and labour will be saved if the patient is first examined to ascertain whether any source of infection is present from which infecting microbes could escape into the intestinal tract. The next question is diet. If possible it is best to examine the fæces when the patient is having a normal diet; purgatives should be avoided, otherwise misleading results may be obtained. Fresh samples of fæces should be examined free from urinary contamination, and the specimens should be collected in clean glass receptacles. Film preparations should be made so as to observe the ratio of gram-negative and positive bacteria, and for the presence of abnormal cells and parasites. Occasionally considerable help may be obtained from an examination of film preparations of the fæces stained by the gram method, as shown by the presence of (1) excessive numbers of large gram-positive bacilli, (2) streptococci, (3) staphylococci, (4) gram-negative bacilli with only a few scattered gram-positive bacteria. For cultural purposes the fæces should be dried on tiles by the method I introduced, and the powder added to appropriate media, which should always include blood agar plates.

Indications for Vaccine Treatment

There are widely distinct groups of cases for which vaccines prepared from intestinal bacteria have been proposed.

(A) Patients suffering from infections which produce a pathological process in the walls of the intestines, such as typhoid and paratyphoid fevers, dysentery, colitis, appendicitis, and localised intra-abdominal suppuration.

(B) Certain conditions, such as rheumatoid arthritis, which has been regarded at times as an intestinal infection, pernicious and other severe anæmias, cutaneous lesions, and certain forms of goitre, to quote but a few examples.

(C) Chronic intestinal toxæmia.

For sake of convenience, I will refer firstly to diseases included in groups (B) and (C). Rheumatoid arthritis is the only one of these conditions I have ever seen benefited from vaccines prepared from the fæces. The treatment of pernicious anæmia with *B. coli* and streptococcal vaccines I consider to be unsound. I have seen patients with pernicious anæmia who have had long courses of treatment with *B. coli* vaccines because it was believed that *B. coli* will produce in rabbits a disease resembling pernicious anæmia. My own observations with strains of hæmolytic and non-hæmolytic *B. coli* have entirely failed to confirm the hypothesis that a disease like pernicious anæmia can be produced in rabbits by inoculation with this microbe.

Hæmolytic streptococcal vaccines are also employed because hæmolytic " streptococci " may be abundant in the fæces or in material obtained from the duodenum in pernicious anæmia. I have tried such vaccines myself, and have seen them used by others, with the result that I am entirely opposed to vaccine therapy in pernicious anæmia. Similarly, I have seen no successful results from vaccine therapy in cases of goitre. It is believed that patients suffering from chronic intestinal toxæmia may be greatly benefited by vaccines prepared from intestinal microbes, but every case, regarded as such, which I have seen was being treated by diet and various drugs at the same time. When hæmolytic streptococci have been found to be numerous in the fæces, in cases of rheumatoid arthritis, sciatica, and general neuro-muscular pains, relief of pain and reduction in the joint effusions has at times occurred following injections of autogenous hæmolytic streptococcal vaccines. In such instances, vaccines should always be prepared from autogenous

strains, as so many varieties of hæmolytic streptococci occur in the fæces. The patients should rest after the inoculations for twenty-four hours, or if there is an aggravation of the patient's symptoms, until these have subsided. There is no such thing as a routine dosage for these patients. Each patient must be considered as a separate unit while he is receiving treatment, and the injections should be increased gradually so as to avoid as far as possible aggravating the condition. If after a most careful trial with an autogenous vaccine the clinical manifestations are increased, then it is unwise to continue further with vaccine treatment. I commence with a dose of 10 millions of a formalised streptococcal vaccine, and I increase the dosage very gradually, usually at weekly intervals, until the correct dosage is obtained. The most satisfactory results occur when pain is relieved and the joint swellings subside, but unfortunately these symptoms may subsequently return, and further vaccine treatment may fail to produce any beneficial effects. I consider, however, that when pain and swelling of joints occurs in rheumatoid arthritis, and abundance of hæmolytic streptococci are found in the fæces, autogenous vaccines should always be given a trial.

We shall now deal with those diseases in which there is a pathological process in the intestinal wall. Typhoid and paratyphoid fevers are dealt with under the general diseases.

Dysentery

I was unable to convince myself during the Great War that vaccines were of any definite value in *acute* bacillary dysentery. Although it has been claimed that Flexner vaccines are of use in the treatment of acute bacillary dysentery in the tropics, and in asylum dysentery in this country, personally I am in favour of postponing vaccine

treatment until the acute illness has subsided. If, however, complications occur such as arthritis and chronic diarrhœa, vaccine treatment should be tried. In cases of this kind autogenous vaccines should be employed, or vaccines prepared from stock strains of Flexner's bacillus of the same type as the infecting microbe, in doses of 20 millions at the outset, for adults, then five days later a dose of 40 millions, and subsequently increasing the dosage according to the results obtained at weekly intervals.

Nolf [1] claims good results in old chronic cases treated with heat-killed vaccines in doses of 1 million up to 5,000 millions. In every case improvement occurred; in some cases an apparent cure was effected, but the patients subsequently relapsed, while in others the cure was permanent.

Autogenous and stock vaccines of *B. shiga* have been employed in a similar manner, and, provided the cultures have been recently isolated, stock vaccines will suffice. It is, however, necessary to employ small doses to commence with, such as 5 million bacilli, to increase the dosage slowly, and to avoid repeating the injections into the same tissue area. In my experience good results may follow treatment with *B. shiga* vaccines in chronic shiga dysentery. Shiga vaccines produce considerable local tissue disturbance, and, as the dosage is increased, a severe general reaction may occur. Attempts have been made to reduce this toxicity by means of formalin, eusol, and by employing sensitised bacilli. There is no question that the ill-effects caused by heat-killed Shiga vaccines are reduced, but by no means lost with formol-killed vaccines.

[1] Nolf, P. (1919): "Vaccine Therapy in Acute and Chronic Bacillary Dysentery," *Journ. Amer. Med. Assoc.*, vol. lxxiii., p. 1177.

Chronic Diarrhœa—Colitis and Septic Infections of the Bowel Wall

The treatment depends on the bacteriological findings. The presence of hæmolytic strains of *B. coli* in the fæces, more especially when an abundant growth of these bacilli is obtained, may be associated with a general toxæmia, together with intestinal symptoms. In such cases treatment with autogenous vaccines has given good results, and complete cure has resulted. Vaccines of hæmolytic colon bacilli are injected in doses of 20 millions, and in five days a further dose is given, and then at weekly intervals in gradually increasing doses. I have given 20 millions of the vaccine, followed by 40, then 50, 75, 100, 200, and so on up to 1,000 and 1,500 million bacilli. The diarrhœa and toxæmia may rapidly subside with such inoculations, although they have been resistant to other forms of treatment. Occasionally vaccines made from non-hæmolytic colon bacilli are of value, but the evidence that these bacilli are the cause of the diarrhœa is difficult of proof.

The mucus capsulatus group may occur in the fæces in large numbers, not infrequently among patients with an abnormal condition of the intestinal tract or a pathological process in the intestinal wall; vaccines can be employed in doses similar to those recommended for colon bacilli.

An excessive growth of non-hæmolytic colon bacilli in the fæces in cases of diarrhœa may be controlled by alteration of the diet and medicinal treatment without the employment of vaccine therapy.

The chief microbes which may be of use for the preparation of vaccines in colitis, chronic diarrhœa, and septic infections of the bowel wall are: (1) hæmolytic *B. coli*; (2) *B. mucus capsulatus*; (3) hæmolytic streptococci, and

in some instances the non-hæmolytic strains ; (4) *S. aureus.* Other bacteria may occur, such as *B. flexner*, but in such instances, if vaccine therapy is indicated, the dosage must be carried out on the same lines as referred to elsewhere in the treatment of such infections.

It may be necessary to employ mixed vaccines of the microbes grouped under (1), (2), (3) and (4) in the treatment of the above-mentioned infections of the intestinal tract.

CHAPTER VIII

INFECTIONS OF THE NOSE, MOUTH, THROAT AND RESPIRATORY SYSTEM

Nose and Nasal Sinuses

The most important infections of the nose and throat which require vaccine treatment are those implicating the various sinuses. One of the golden rules in vaccine therapy is brought home very forcibly if during vaccine treatment the drainage of an infected sinus becomes obstructed, for in these circumstances a violent reaction usually follows. In a case of sepsis of the frontal sinus with unsatisfactory drainage, when vaccine treatment is employed, an inflammatory reaction may occur in the tissues around the exit with violent increase of headache and other symptoms. From experience of these cases, I never treat a case of sinus infection with vaccines until drainage is fully established and remains so during the course of the treatment. Many cases of sinus infection are greatly aggravated by failure to recognise this rule, to which there are no exceptions. Once drainage is established, but progress in the patient's condition is unsatisfactory, then an autogenous vaccine should be tried. It is a mistake to employ vaccines until the nature of the infection is known, as it is not uncommon to obtain a mixed infection with two or more microbes, and when the infected material has been held up in the sinus for some time the bacterial content may be very considerable. The commonest microbes met with are pneumococci, *S. aureus*, non-hæmolytic streptcocci, and hæmolytic streptcocci less

frequently; the *B. mucus capsulatus* group and *B. influenzæ*. Other microbes may occur, but these are the most important. A patient whom I saw several years previously for an acute *B. coli* infection of the urinary tract developed a similar infection of the nasal sinuses. Vaccine treatment is also required in cases of sinus infections for those patients who develop arthritis. The vaccine should be given in doses of 10 to 20 millions of each microbe at the outset; then the dosage is increased gradually at weekly intervals as circumstances permit. If an attempt is made to treat a complication such as arthritis, the dosage should be very gradually increased so as to avoid aggravation of the clinical condition. In very chronic cases of sinus infection it is uncommon to obtain much improvement from vaccines, whatever dosage is employed.

Leprous and tuberculous infections of the nose are treated with vaccines on the same lines as described for infections of the skin in Chapter IX.

B. mallei infections of the nasal passages occur in man occasionally, but vaccine treatment is of no avail.

Carrier cases of diphtheria of the nose and throat have been treated with vaccines, but in my experience without effect.

Mouth

It is not my intention to enter into the numerous controversial discussions which have gathered around the various infections included under the term "oral sepsis." It is necessary firstly to consider whether vaccine therapy is of value for any of these infections in the mouth, and secondly whether it can be employed for the treatment of rheumatoid arthritis and neuritis, which may be dependent upon such an infection. Opinions apparently widely differ as to the value of vaccine therapy for the

treatment of pyorrhœa alveolaris, gingivitis, and suppurative processes of the gums and tooth sockets. My own opinion is based upon many years' personal experience of the treatment of these infections with autogenous and stock vaccines, and from an examination of cases treated by others, but I have never seen a result which indicated that vaccine therapy had been of the slightest use. Patients, however, who are suffering from arthritis, periarthritis, neuritis, and lumbago believed to be dependent upon an infection of the gums, or in and around the tooth sockets, may be greatly benefited by vaccines prepared from the bacteria isolated from the infective process in the mouth. The condition of the mouth should be carefully observed, and an X-ray examination of the teeth by a radiologist with considerable experience of dental radiology is essential. If there is an indication of active infection of the lining membrane of the tooth sockets and surrounding bone, cultures should be taken from the apex of an infected tooth socket at the moment of extraction and from the fangs of the tooth as well. It is in cases with "closed sepsis," or, in other words, when drainage is impossible, that arthritis and neuritis especially occur. The important microbes met with from this source are streptococci, hæmolytic and non-hæmolytic, *S. aureus*, and very occasionally pneumococci. In some cases pure cultures of long-chained hæmolytic streptococci are obtained, and in other cases pneumococci. Vaccines should be given in small doses, beginning with 10 to 20 million cocci, and the dosage is increased gradually at weekly intervals. It is important to so regulate the dosage that an increase of pain and swelling in or around the joints is avoided. If there is insufficient drainage of the infected tooth area then the arthritis or other complication may be aggravated

by vaccines. Cases of sub-acute infective endocarditis have also been treated with vaccines prepared from microbes isolated from the tooth sockets, but I have seen no benefit ensue from these vaccines as recorded in the paragraph on this subject in Chapter V.

Recurring Colds

Considerable benefit from vaccine treatment may be obtained from autogenous vaccines and sometimes from stock vaccines. In some cases cultures are taken from the posterior nares on long post-nasal swabs, in others from the tonsils and throat, and in others from the sputum, according to circumstances. The material should be plated out on blood agar and hæmoglobin agar (chocolate agar). Mixed vaccines are generally necessary, as the infections are commonly multiple. The bacteria usually isolated are pneumococci, influenza bacilli, streptococci, hæmolytic and non-hæmolytic, *B. mucus capsulatus*, and *S. aureus*. If a mixed vaccine is to be given it is best to employ each microbe at the outset in doses of about 15 millions, and to increase the dosage at weekly intervals. It is generally advisable to withhold the vaccine until the acute stages have subsided.

Examination of Sputum

The sputum is collected in sterile bottles after the mouth has been washed out. It is then examined bacteriologically by Dudgeon's method, *i.e.*, dried on unglazed porcelain tiles, and the dried powder spread on the appropriate media, which should include blood agar and hæmoglobin chocolate agar.[1] All samples of sputum should be examined at the earliest moment after expectoration, and the tubercle bacillus should always be looked for.

Bronchitis

Some of the best results in vaccine therapy are obtained in cases of bronchitis, more especially the recurring form associated with the expectoration of thick muco-pus. Such cases, when due to *S. aureus*, and pulmonary infections due to this microbe are much more frequent than is usually taught, may improve rapidly and to a remarkable degree with vaccine treatment. I commence with a dose of 20 millions for adults, and increase the dosage at weekly intervals. Patients suffering from this form of infection often fail to improve until vaccine treatment is adopted. As a rule, these patients, especially asthmatics, are very sensitive to vaccines of *S. aureus*, until there is considerable reduction in the amount of expectoration and in the viscosity of the thick muco-purulent sputum. Vaccine therapy should be employed on the same lines for infections due to pneumococci, streptococci, and influenza bacilli which do not respond to ordinary treatment, and for cases which relapse. In cases of mixed infection the inoculations should be carried out at weekly intervals, always commencing with doses of about 15 to 20 millions of each microbe.

[1] Purulent sputum should be plated direct without drying.

If after six injections there is no apparent improvement, either in the patient's general condition, or in the quantity or quality of the sputum, it is improbable that any improvement is likely to occur from a prolonged course of vaccine therapy. It is impossible to dictate the rate of increase in the dosage, as every patient has to be considered on his or her own merits, and it also depends on the amount of expectoration, but, as a rough guide, if the first dose given was 20 million pneumococci, and the improvement in the patient's condition is satisfactory, then the dosage should amount to about 300 million cocci at the fifth or sixth injection. In all such cases autogenous vaccines should be employed.

Chronic Bronchitis and Bronchial Asthma

Cases of chronic bronchitis frequently improve to a very considerable extent when treated with autogenous vaccines more especially those cases of chronic bronchitis following upon a previous acute attack. A bacteriological examination of the sputum should be made from a typical sample as judged by naked-eye examination. In every instance blood agar and hæmoglobin chocolate agar should be employed as a routine procedure, and if the latter medium is employed in cases of chronic bronchitis associated with fibrosis of the lung, an abundant growth of influenza bacilli may be obtained. The usual bacteria obtained from the sputum in cases of chronic bronchitis are streptococci, hæmolytic, non-hæmolytic and pneumococci, *B. influenzæ*, *B. mucus capsulatus*, *M. catarrhalis*, *S. aureus*, and diphtheroid bacilli. If a mixed vaccine is required, it is safe to begin with a dose of about 10 to 20 millions of each organism, and if the patient after five or six doses fails to show definite improvement, it is more satisfactory to make a fresh bacteriological examination

of the sputum, and to prepare another vaccine rather than to persevere with a vaccine which apparently has failed. The injections are made at weekly intervals, the dosage should be increased very carefully, and autogenous vaccines are essential. In cases of chronic bronchitis associated with asthma, the sputum may be very viscid or in tight masses, with a large quantity of watery exudate, or strings of mucus may be mixed with the fluid portion of the sputum, or, if complicated by an acute attack of bronchial inflammation, true pus may be present. A bacteriological examination of sputum showing any of these appearances usually gives a growth of non-hæmolytic streptococci. Patients suffering from chronic bronchitis and asthma with a watery mucoid or tenacious sputum may derive considerable benefit from a course of autogenous streptococcal vaccine. The treatment of patients suffering from asthma, however, with bacterial vaccines requires considerable care, as although some cases benefit considerably from *small doses* of vaccines, yet they are quite unable to withstand a dose of more than 50 to 100 millions at any period of the vaccine treatment. I have known cases which could not tolerate more than 50 million cocci, and in the case of a man who received three courses of autogenous vaccines for two successive years, the maximum dosage which he could tolerate was 50 millions cocci.

Broncho-Pneumonia. Abscess of the Lung

In broncho-pneumonia, once the acute stages of the disease are passed, autogenous vaccines prepared from the sputum may be tried, and sometimes may prove of service in hastening recovery. The first dose of the autogenous vaccine for adults, as in the case of bronchitis, should be about 15 millions.

I have treated with autogenous vaccines prepared from the sputum a few cases of localised abscess of the lung, but in each case without success. The last patient so treated had a large localised abscess in the right lung from which an abundant growth of a long-chained hæmolytic streptococcus was isolated. The injections were made with a vaccine prepared from the organism, at weekly intervals, but after a very full and thorough trial it was found that the patient's health was in no way benefited, and as the vaccine had apparently increased the frequency and intensity of the attacks, this treatment was abandoned. The probable explanation of the failure obtained by vaccine treatment was that the reaction produced in the inflamed mucous membrane of the bronchial tube, or tubes, leading from the abscess cavity was such that the infected sputum could not be expectorated in a satisfactory manner.

Bronchiectasis

I have never seen any cases benefited from vaccine treatment, which is only to be expected, judging from the pathological processes found in this disease.

Tuberculosis

The treatment of cases of pulmonary tuberculosis fall into two main groups : (1) Those who are to be treated with a tuberculin preparation only ; (2) those who are also to be treated for superadded mixed infections. For cases of the second group autogenous vaccines of streptococci, pneumococci, or other pyogenic bacteria are prepared from the sputum and are inoculated at weekly intervals, as in the case of non-tuberculous patients. It is essential to keep a careful record of a patient's weight and temperature during such treatment, so as to control the dosage and to avoid excessive tissue reaction. The treatment of pulmonary

tuberculosis with tuberculin should only be adopted when the patient is under the routine of sanatorium treatment, or when careful observations can be made by those experienced in the treatment of pulmonary tuberculosis. To treat an individual case without proper control is to court disaster. Statements made about new preparations of tuberculin which are credited with a high percentage of " cures " or even good results, should always be received with the utmost caution. My own experience of the treatment of pulmonary tuberculosis with tuberculin is too limited for me to express a positive opinion on the subject, but such advice as I have already given may prove to be helpful.

Empyema

Cases of empyema, once they are efficiently drained, may improve with autogenous vaccines, which should be prepared from the organisms in the pus at the time of aspiration. The dosage is on the same lines as in other infective processes already referred to. Drainage, however, must be efficient during the whole of the treatment.

Actinomycosis

In actinomycotic lesions of the chest wall, pleura, or lung, vaccine therapy has been recommended by Colebrook.[1] Vaccines are prepared from cultures of the streptothrix, which are broken up so that the emulsion can be injected as an ordinary bacillary vaccine. Colebrook ummarises his views on this subject as follows : " The treatment of actinomycosis by vaccines facilitates recovery when efficient surgical drainage of the affected tissues is secured and maintained ; when, however, drainage is unsatisfactory, the use of appropriate vaccines will not usually suffice to stay the progress of the infection."

[1] Colebrook, L. (1921) : " A Report upon Twenty-five Cases of Actinomycosis, with Especial References to Vaccine Therapy," *Lancet*, April 30th, vol. i., pp. 893–899.

CHAPTER IX

INFECTIONS OF THE SKIN AND CONNECTIVE TISSUES, AND OF THE BONES AND JOINTS

Acne Vulgaris

This disease is an infection of the sebaceous glands, and is one of the commonest infective processes of the skin. According to my own experience of this disease, four varieties occur, which are referred to here, together with their distinctive features, both clinical and bacteriological.

1. In the suppurative form of acne, *S. albus* is present in pure culture or is the predominant microbe, but occasionally *S. albus* and *S. aureus* occur together.

2. The type characterised by red inflammatory papules in the skin, which may not reach the suppurative stage. From these pure cultures of *S. albus* or *S. albus* together with acne bacilli are obtained.

3. The type in which indolent " blackheads " occur, or inflammatory processes in the skin around the " blackheads " ; *S. albus* is cultivated alone or together with the acne bacillus.

4. The type in which there are small or large pockets in the skin which contain thick sebaceous material, with an offensive odour, or with inoffensive mucus-like material. The contents of such lesions may be found to be sterile, or may contain *S. albus* alone or together with the acne bacillus.

While at the present day it is the custom among certain

members of our profession to express considerable doubt as to the efficiency of vaccine treatment for acne, my own opinion is very strongly in favour of vaccine therapy, but not all cases will respond to this mode of treatment. I have seen patients treated by all other possible means without improvement who have rapidly responded to treatment with vaccines. The great difficulty is to know the kind of cases which may be cured or benefited by vaccine therapy, and those for whom vaccine therapy is likely to be of little or no avail. I consider the best results are obtained among cases included in group 1. Group 2 cases are difficult to treat on the whole, while the indolent cases referred to in group 3, if they remain indolent in spite of a few doses of a vaccine, are not likely to benefit in any way. Those cases referred to in group 3, in which there is inflammation around the " blackheads," are likely to benefit from vaccine therapy. Cases included under group 4 are seldom benefited by stock vaccines of *S. albus*, *S. aureus*, or acne bacilli, or from autogenous vaccines if such are possible. The worst cases are those which show extensive involvement of the skin of the back, and when the skin is very greasy. My experience is at variance with published records, as I have only obtained good results in the treatment of acne vulgaris with autogenous or stock vaccines of *S. albus*, and occasionally with *S. aureus* when the *S. albus* vaccines have failed. Vaccines prepared from acne bacilli have invariably been disappointing unless combined with *S. albus* vaccines. I always adopt the following methods when treating cases of acne : At the commencement of treatment autogenous vaccines are employed, when possible, but if these fail, then stock vaccines of *S. albus* are tried, and lastly stock vaccines of *S. aureus*. Some observers employ vaccines of colon bacilli made from strains of this microbe isolated

from the fæces, but I have had no experience of this line of treatment, and cannot see any reason to justify it. Very occasionally rapid improvement in very obstinate cases has occurred after a strong reaction produced from the injection of one or more large doses of typhoid vaccine.

With regard to the question of dosage, there is no doubt that this is of the utmost importance in the vaccine treatment of cases of acne, as some cases rapidly improve on very small doses at weekly intervals, while other cases require large doses. Therefore, it is necessary to treat every case at the outset with small doses of 10 to 20 millions of each microbe employed in the vaccine at weekly intervals, and to increase the dose gradually. If no improvement occurs from small doses, then large doses of from 500 to 1,000 millions or more may be employed ; if there is still no improvement there can be no doubt that the vaccine which has been employed is useless. Further vaccines should be tried, for if the correct case has been selected for treatment, improvement or cure may occur from the administration of another vaccine. With some patients no effect occurs until stimulation of the focal areas is produced by local applications, so as to improve the tissue circulation. I have found that by such means, in conjunction with vaccines, a definite improvement has followed, although vaccine treatment alone had failed. The skin stimulation may be affected by light treatment, but not infrequently certain stimulating ointments are sufficient.

In conclusion, it is well to remember that during vaccine treatment for acne, it is essential to open inflammatory areas of pent-up fluid, to attend to the patient's diet as required, and to treat constipation, or any other derangement, as may be necessary.

Furunculosis and Carbuncles

In the vast majority of cases furunculosis and carbuncle are caused by *S. aureus* in pure culture, although streptococci may be present also in carbuncles, while in styes *S. albus* often occurs with *S. aureus*. The essential organism for vaccine treatment is the *S. aureus*. Of the conditions referred to at the commencement of this section, it is essentially for furunculosis that vaccine treatment is necessary and to a less extent for cases of styes and sycosis, but as the conditions known as perinephric abscess, lymphangitis, sycosis, and stitch abscess are *S. aureus* infections, the same treatment may be followed in these conditions as will be described in detail for furunculosis.

Of all infections, probably " boils " yield better results with vaccine treatment than any other, and in spite of the modern enthusiasm for certain colloidal and other preparations of various metals, the results obtained with autogenous and stock vaccines are often remarkable, provided the correct line of treatment has been adopted. Autogenous vaccines can be prepared from the pus of the lesions, or stock vaccines of *S. aureus* may be employed at the outset, and if these fail, autogenous vaccines can be utilised at a later date. The dosage to commence with is usually about 25 millions, and five days later 50 millions, and then at weekly intervals increasing the dosage as circumstances demand, so that after eight injections the patient is receiving about 1,500 million microbes. It is not an uncommon experience for small " boils " to appear at the commencement of vaccine treatment which do not suppurate, and after two or three days resolve as rapidly as they appeared. Closed boils containing pus should be opened, otherwise the focal process will extend, and this

is especially likely to occur during vaccine treatment. If one course of eight to ten injections of a stock vaccine fails, a second course should be carried out four to six weeks later with an autogenous vaccine. Cases occur which continue to relapse in spite of adequate vaccine treatment, but such cases may rapidly respond to one or two injections of a beef broth bacteria-free filtrate obtained by growing *S. aureus* for one month at 37° C. Dr. Bamforth and I [1] tried similar filtrates for our *S. aureus* precipitin reactions. In these cases I have given an injection of 0·25 c.c. subcutaneously, followed when necessary in seven days with 0·5 c.c., but, owing to the severe local and general reactions which may occur, it is necessary to fully explain to patients that a widespread urticaria, pyrexia, and general malaise may follow this form of inoculation treatment, which may continue for one to three days.

When I first employed this method of immunisation, which corresponds to what is generally known as "phylacogen therapy," it appeared to me that as the reactions were so severe it was suitable only for cases which had resisted other methods of treatment. Mixed "phylacogens" which are bacterial-free filtrates of varous microbes have been employed for the treatment of infective processes of recent years, but the filtrates which I employ are prepared from one strain of *S. aureus*, as already described, and have only been used for *S. aureus* infections. I have seen three cases of boils which had been treated by vaccines and other methods for considerable periods without success, yet these patients were rapidly cured by subcutaneous injections of bacterial-free *S. aureus* filtrates. I

[1] Dudgeon, L. S., and Bamforth, J. (1925): "On Staphylococcal Precipitin Reactions in Cases of Acute and Chronic Infections, and also in Serum Sickness," *Journ. Hygiene*, vol. xxiii., No. 4.

will now refer to two very remarkable cases of skin suppuration. The first case was one of multiple abscesses in the skin and subcutaneous tissues in a patient who was injecting herself with morphia. These abscesses contained either blood-stained pus, or thick muco-pus, which showed evidence of old hæmorrhage, and they occurred at the sites of the needle punctures. Pure cultures of *B. proteus* were obtained from them, and when an autogenous vaccine was given in conjunction with puncture and drainage of the abscesses, complete cure of the infective process resulted. The second case was also a woman, who had cystitis due to *B. coli*, and had some seventy abscesses in the abdominal wall, which were proved to be due to the same strain of *B. coli* as present in the urine. It was found that they were due to direct inoculation of the skin by the patient with her infected urine. She was treated with an autogenous vaccine with a satisfactory result.

Carbuncles.—The treatment of carbuncles by vaccine therapy is a question which causes wide divergence of opinion, as some advocate it, while others are directly opposed to it. I consider that vaccine treatment is *contra-indicated* when the inflammatory process is *acute and progressive* and if there is little or no drainage : but if the carbuncle is indolent, and the tissues show little sign of reaction, then small doses of *S. aureus* vaccine can be given at weekly intervals. If streptococci are present in the pus it is advisable to employ a mixed autogenous vaccine of *S. aureus* and the streptococcus. If too large a dose is given, or the injections are repeated at too short an interval, then active increase of the symptoms may develop, and local extension of the carbuncle, so that considerable harm may occur in the treatment of carbuncles from lack of knowledge of vaccine therapy. It is also well to avoid the

use of vaccine therapy if violent surgical measures are to be perpetrated. It has been recommended that the vaccine should be injected in the vicinity of the carbuncle, but there is no adequate reason for this line of treatment. Vaccine therapy is most efficacious in those infective processes when there is ample free drainage, but the tissues show little or no tendency at repair, just as it is contra-indicated before drainage is established, and when the inflammatory process is spreading.

Cutaneous Lesions

Without employing the various technical terms used by dermatologists, cases which are likely to benefit from vaccine treatment are those with suppurative lesions from which *S. aureus*, *S. albus*, or streptococci are cultivated. It is always necessary to make a bacteriological examination of the pus before stock vaccines are employed, and if patients have failed to respond to stock vaccines, autogenous vaccines should be prepared.

Lupus

In cases of lupus with well-marked ulceration, improvement may follow treatment with tuberculin T.R. or B.E., or with emulsions of tubercle bacilli made in a similar manner to ordinary vaccines, as already referred to. If a secondary infection is present, an autogenous vaccine of the pyogenic microbe may be given with the tuberculin about every seven days. Vaccine therapy should be combined with other treatment required for cases of tuberculosis. It is necessary to exclude pulmonary tuberculosis before commencing tuberculin treatment, so as to avoid any risk that may arise from large doses of tuberculin.

Leprosy

James Hasson [1] has introduced for the treatment of leprosy a stock vaccine of *B. pyocyaneous* of 15,000 millions, and about 5,000 millions of *B. lepra* in 2 c.c. of normal saline. The lepra bacillus is obtained from blister fluid induced by carbonic snow according to the method of Hasson. The blister fluid from various cases of leprosy, whether nodular or anæsthetic, or mixed, is incubated at 36° *C. only* for from fifty to ninety days. The cultures of *B. pyocyaneus* are also mixed and added to the serum containing the lepra bacillus, which has been prevented from clotting by the addition of sodium citrate. The injections are given either intravenously or subcutaneously, but while the former method incites violent reactions, the latter produces only a very slight febrile reaction. According to Hasson, after three injections, the nodules flatten and disperse, and the areas of anæsthesia disappear at the end of two to four months. Such results are indeed remarkable, and, if confirmed, would reduce the seriousness of leprosy to that of a mere trifling infection. Personally, I have had no experience of this method. In the same number of the *Transactions of the Journal of Tropical Medicine*, Row [2] claims good results in the treatment of leprosy with a vaccine of so-called "autolysed" tubercle bacilli. This vaccine consists of autolysed cultures of tubercle bacilli which have been washed with petrol ether to remove fatty substances. The injections are given subcutaneously at weekly intervals in doses of 0·025 mgm. of the autolysed tubercle bacilli for five months or longer.

[1] Hasson, James (1926): "A New Method of Diagnosis and of Vaccine Treatment in Leprosy," *Trans. Roy. Soc. Trop. Med. and Hygiene*, vol. xix., No. 7.

[2] Row, R. (1926): "Treatment of Leprosy by a Vaccine of Autolysed Tubercle Bacilli," *Trans. Roy. Soc. Trop. Med. and Hygiene*, vol. xix., No. 7.

There is no local, focal, or general reaction. The results obtained by Row, although not expressed in such optimistic terms as those of Hasson, certainly indicate that a full trial should be given to this method of treatment.

Acute and Chronic Osteitis and Arthritis

In acute osteitis, until drainage is established, vaccine therapy is *contra-indicated*. In acute osteitis, with efficient drainage, and in chronic suppurative osteitis, vaccine treatment is required if the condition fails to improve in spite of efficient surgical treatment. Autogenous vaccines should be prepared and given at weekly intervals. If increased pyrexia and pain occur during the course of vaccine therapy, provided excessive dosage has been avoided, the probable reason is insufficient drainage, indicating that the infected material is pent up. Under such circumstances, no further injections should be given until drainage has been re-established. Exactly the same remarks apply to acute and chronic septic arthritis.

Gonococcal Arthritis

In the treatment of gonococcal arthritis much divergence of opinion exists. Some consider gonococcal vaccines as useless or even harmful, others that these vaccines are of the utmost value, and others that the best results occur from the injection of substances which produce so-called protein shock. Further, it has been the fashion to abandon ordinary gonococcal vaccines for sensitised vaccines and, more recently, for detoxicated vaccines. Gonococcal vaccines can be administered in cases of acute gonorrhœal rheumatism, but only in very small doses of about 5 million cocci to commence with, and a second injection five days later provided there is no extension of the disease. The strength of the vaccine should be gradually increased

on each occasion, and an interval of one week should be allowed between the injections. My experience of gonococcal vaccines is that they should be reserved for cases of chronic gonorrhœal rheumatism. In these chronic cases there is much less risk of aggravating the condition, and larger doses of vaccine can be given. The first dose of gonococcal vaccine should be about 10 millions, and the injections are given once a week in increasing amounts. In the acute cases it may be possible to employ autogenous vaccines, but in the chronic cases stock gonococcal vaccines made from several strains of gonococci are usually given. It is essential for patients during vaccine treatment to be at rest for twenty-four hours or longer after the injections. In chronic cases it is best to realise that vaccine treatment will have to be continued over a prolonged period, and to make no attempt to increase the doses too rapidly, or to shorten the intervals between the injections. Some observers have recommended large doses of gonococcal vaccine so as to produce a definite reaction in the joints, but in my opinion such methods should not be attempted. For cases which resist all other forms of treatment, protein shock has been employed, but my experience of this method is so limited that I am unable to express and positive opinion as to its value. The evidence derived from the literature, however, would indicate that it is only in an experimental stage.

Rheumatoid Arthritis

The treatment of cases of acute and chronic rheumatoid arthritis by means of vaccine therapy is discussed in the various sections on septic infections, but cases of rheumatoid and osteoarthritis have been treated with vaccines prepared from microbes isolated from the joints and bones.

Tuberculosis

In the treatment of tuberculosis of bones and joints with tuberculin, it must be clearly understood that such treatment is merely to be an adjunct to hygiene and surgery. One of the forms of tuberculin, such as T.R. or B.E., or an emulsion of dead tubercle bacilli is given at weekly intervals, and in such dosage as to obtain only very mild focal reactions. In the old days of mixed infections, due to errors in the surgical treatment, pyogenic vaccines were sometimes of use, but I have not employed such a vaccine since 1912.

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