A Lecture

ON

THE PRINCIPLES INVOLVED IN PROPHYLAXIS
AND THERAPY BY MEANS OF VACCINES.*

BY

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HAD my subject been merely that of prophylaxis by means of vaccines, I should have felt myself in a fairly strong position in coming before you, as prophylaxis rests on strong scientific foundations, and has in practice proved its merit. I must, however, claim your indulgence in my discussion of vaccine therapy because my clinical experience of it has been strictly limited and my interest in it has been largely confined to the immunological problems it offers. On the other hand, I take refuge in the reflection that, though vaccines have been exploited in treatment for, I should say, over twenty years, the accumulated clinical data as to their efficacy or otherwise have not yet supplied that decisive link in the evidence which would raise vaccine therapy from the level of a purely empirical practice. What I mean is that any scientific basis on which specific vaccine therapy may rest has not been enlarged and built upon by decisive experiment on man or animals, and the consequence has been that vaccine therapy continues on its hapless way, exploiting now this, now that purely technical modification, but really in no way consolidating its position as the form of specific therapy which it has been believed to be.

I would explain how the matter appeals to me, regarding the introduction of bacterial vaccines solely as a means calculated to raise the natural defences of the body, and really based on immunological experiment, but gone somewhat astray in its application to therapy. I propose, therefore, to disentangle from the ravelled accumulation of data on vaccines just those elements which rest on experimental fact. I do so in the hope that the practitioner may be constrained also to test his vaccines and interpret his results in such wise that he will gain comparative knowledge from the experience. I freely admit that in general practice conditions are far from suitable for procuring reliable comparative statistics with regard to the efficacy of vaccines, or in fact of drugs generally. Only few have the time or inclination to amass comparative statistics that may mean real additions to knowledge, but I believe much may be gained by frank discussion of the effects which vaccines are claimed to produce in therapy, and this I propose to do. Let me, then, trace briefly the origin and development of the use of vaccines in prophylaxis and therapy, confining myself solely to experimentally ascertained facts. I start naturally with prophylaxis, and may probably end with prophylaxis, because I hope to show that much of what is called specific vaccine therapy is simply a form of prophylaxis, and what is not prophylaxis is simply a form of non-specific protein therapy—bacterial protein therapy if you like, it is immaterial.

PROPHYLAXIS BY VACCINES.

Prophylaxis of infectious disease by means of vaccines I must deal with only shortly, as, apart from vaccination against small-pox, the method does not enter largely into the sphere of the general practitioner, at least in this country. The use of the living attenuated virus remains with us only in the prophylactic methods developed by Jenner and Pasteur against small-pox and hydrophobia. In certain veterinary diseases, however, the methods of Pasteur, or modifications of them, still find practical application, and there would seem to be little doubt that only by means of the attenuated live viruses is it possible

to secure solid immunity against certain highly virulent infections in highly susceptible animals. The axiom that the live virus is the one most calculated to give solid immunity as tested experimentally by a lethal dose method is not to be lost sight of in the prophylaxis by dead vaccines of human bacterial infections. In a recent Harben lecture I have discussed the position of enteric fever prophylaxis, which was worked out almost solely on data concerning antibody production in animals (especially bactericidins) elicited by typhoid antigen. We now know that immunity, as measured by capacity to withstand an otherwise lethal dose of infection, is not necessarily correlated with the antibody content titratable *in vitro*. The fundamental difference between an immunized animal whose antibody content has fallen to normal levels and an untreated normal animal is that in the former the injection of a minute dose of antigen elicits a prompt and massive response of the antibody mechanism, whereas in the latter the response is slow and meagre. Some doubt has been expressed of late as to whether we can hope with dead vaccines to secure that degree of immunity which the attenuated virus can afford. The question can be answered only by animal experiment. Even though the causative agents of human disease, such as the enteric and paratyphoid fevers, cholera and dysentery, cannot reproduce with any exactness the symptom-complex of the human disease, they possess sufficient pathogenicity to make the lethal dose test of immunity a valuable criterion of the immunizing capacity of antigen. It is believed by some workers that the defects of the killed antigen can be made good by increase of dose. This may prove to be so, but at the present time new ground is being opened by advances in our knowledge of bacterial variation, and the choice of a suitable variant as the source of antigen may become the all-important factor in securing solid immunity with killed vaccine.

VACCINE THERAPY.

Vaccine therapy was in its origin really a development of vaccine prophylaxis applied to the more chronic types of infection. We must go back a little more than twenty years to find bacteriologists and clinicians eagerly investigating the claims of opsonic index determinations as guides to the state of immunity of the individual, whether normal or infected. It had been known that while certain organisms like the typhoid bacillus or the cholera vibrio were susceptible to lysis in the presence of immune serums, such organisms as the staphylococcus or the streptococcus, and many others, were not killed in the presence of serum prepared from animals immunized with these organisms. Denys and Leclef, however, found that when organisms like the staphylococcus or streptococcus were placed in contact with leucocytes and immune serum they were eagerly phagocyted. Some substance in the immune serum, to which the name "tropin" or "*substance sensibilisatrice*" was given, prepared the organism for phagocytosis by the leucocyte.

Opsonins.

Later Wright and Douglas showed that normal serum contained a body having the same property, and though the new name of opsonin was coined for it, it was demonstrated, as the result of much experiment devoted to the question, that the normal opsonin was in no way separable from the immune opsonin in structure and function. The name, however, has stuck, and it is quite a good name. Wright decided that the estimation of opsonin in the infected individual might afford an index of the degree of immunity in staphylococcal infections just as the bactericidal power of the serum had been used as a guide in estimating the development of immunity to *B. typhosus*. The method failed as a practical guide in immunization, and, I think, has been entirely given up. Its failure was largely due to the fact that it was overexploited as a practical guide and scientific claims were made for it as a quantitative index of immunity which were not merited. Moreover, at the time, it was not realized that non-specific factors entered largely into the matter, leading either to rise or depression of the opsonin content. I shall come to this presently.

* Delivered to the Croydon Division of the British Medical Association, February, 1926.

One point on which great stress was laid was the occurrence of a negative phase after the injection of a vaccine, and much was made of the alleged dangers of producing too severe negative phases by overdosage and of the alleged lowered resistance of the individual during these phases. It was noted that after a dose of vaccine there was a primary fall in the index followed by a rise, reaching its acme about the end of the first week. Now we know that a temporary fall in antibody follows regularly the introduction of a dose of antigen. It is probably to be explained on physico-chemical grounds as one of the effects following the injection of a colloid. It cannot be adequately explained as the result of abstraction of antibody by the antigen injected. This fall in the opsonic titre Sir Almroth Wright brought into relation with certain focal or general reactions liable to occur at early periods after the administration of a vaccine. Thus, to take an example from his *Studies in Immunisation*: A patient suffering from boils was given a dose of staphylococcal vaccine. On the following day the patient's phagocytic power was found to be reduced. "Contemporaneously with the development of this 'negative phase' an irritable pimple developed on the neck. We may see in this, for it is a phenomenon which has manifested itself again and again in connexion with our inoculations, an indication that the negative phase is associated with a diminished resisting power to invasion by the staphylococcus." I dare say the phenomenon of focal reaction is well known to all of you.

From such considerations as these was built up a practice of immunization which was regarded as applicable with safety to the patient only when the system of dosage was controlled by periodical estimations of the opsonic index. Only the trained immunizer was to be entrusted with the task. Now we know, of course, that fearful things did not happen when the opsonic control was left out. Further, it came to be realized that variations in opsonic content bore little or no relation to the clinical state which is all we have to depend on for an estimate of the host's reaction to an existing infection. However, I may say that for a good many years now therapeutic immunization has proceeded on certain fairly stereotyped lines, commencement being made with doses of a killed organism which experience has shown to be relatively innocuous and passing on at fairly uniform intervals to larger doses, the only guide to treatment being the patient's responses and common sense.

I do not propose to discuss the value and results of this alleged specific therapy. I can only repeat what I have been credibly informed—namely, that in certain more or less acute infections like furunculosis, where the effect of any treatment can be very correctly estimated, vaccine treatment has in the main made good. Vaccine treatment of furunculosis might probably rank as a specific therapy, but not as a specific staphylococcal therapy seeing that vaccines of *B. coli* or of *B. typhosus* have been shown to act similarly on furunculosis. In other types of chronic infection—for example, chronic gonococcal infection or bacillary cystitis—vaccine therapy may claim to exert specific action, but it is doubtful whether there is any unanimity among clinicians on the point, and we have no other source of precise information.

When we consider, further, the many other forms of chronic infection, such as the respiratory and arthritic affections, in which vaccine therapy is widely used, we feel ourselves to be almost entirely in the realm of pure empiricism because we have no certain knowledge of the etiology of these infections. In the respiratory group recourse is had to vaccines prepared from the mixed flora multiplying and presumably doing harm in the affected region. In arthritic affections, again, it may be expedient to prepare vaccines from organisms vegetating in situations still more remote from the clinical side of the trouble—for example, from faecal streptococci—on the chance that they may be concerned with so-called intestinal intoxication, which again may be associated with, shall we say, rheumatoid arthritis. In fact, all we can really say about such vaccines is that they consist of bacterial protein. Now we know that, apart from antibody response, the introduction of bacterial protein into the body is followed by a chain of intensely

interesting physiological phenomena; some of these I propose to discuss, so that we may get back to really basic principles. The first point I must make is that vaccine therapy does not lend itself readily to experimental investigation in the laboratory. Chronic infections which would afford scope for therapeutic treatment by vaccines are not easily induced, with the notable exception of tuberculosis. Acute infections in laboratory animals are usually too acute and of too short duration to render vaccine trials possible. We have therefore to resort to experiment on normal man and animal, determining the effects exercised by bacterial protein injections on antibody content, the fluid and cellular constituents of the blood, body temperature, blood pressure, etc.

Non-specific Protein Therapy.

On these points a mass of data is now available which helps us to understand something of the mechanism of action of bacterial protein when introduced into human beings. Let me go back to the days of the opsonic index. An investigation I then undertook, in collaboration with Professor W. Bulloch, was on the influence of experimental leucocytosis on opsonic content. Of various substances employed to produce a leucocytosis experimentally, such as nuclein, sodium cinnamate, tallianine, etc., the first mentioned was the only one which in addition produced a very notable temporary increase in opsonin (50 to 100 per cent.). This increase made its appearance within an hour of injection, and was generally gone by twenty-four hours. It was entirely a non-specific rise, and quite irrespective of the organism employed to demonstrate it. Also autolysed bacterial protein had the same effect as nuclein. The phenomenon was later investigated by Bedson, but it was found impossible to explain it in terms of increased amboceptor or of complement. It is highly probable, in the light of later work with colloids, that this prompt variation in normal antibody following the introduction of substances like nuclein, or any autolysed bacterial protein, comes into the category of those purely physiological phenomena which the injection of a colloid can induce. In any case, it was this apparently non-specific early variation in antibody induced by nuclein and autolysed bacterial protein which led me to believe that many of the immediate effects of vaccines, such as the early euphoria, the sometimes startling clinical improvement, and the focal and general reactions, were disturbances which had their source in the colloidal nature of the vaccine.

I may say that while this view has long been held by many immunologists it will have been observed that only recently Sir Almroth Wright has thrown overboard the principle of specific vaccine therapy in the old sense, at least so far as the treatment of acute septicaemic infections by vaccines is concerned. His method of immunotransfusion is, in part at least, an attempt to administer passively to the patient the antibodies which the injection of substances like nuclein or bacterial protein can rapidly induce in a normal person. We have, however, a large body of evidence on the point. It was noted many years ago that an intravenous injection of typhoid vaccine in typhoid fever frequently brought the temperature down promptly and the febrile state ceased, leading to rapid convalescence. Soon, however, came the demonstration that an injection of *B. coli* vaccine, or indeed of substances like casein or deuterio-albumose, could do precisely the same thing in typhoid fever. The exact mechanism is not yet understood. We know that in the normal animal a pyrogenic effect is produced by the intravenous injection of a minute quantity of bacterial protein. It is suggested that when a similar injection is made in a case of typhoid fever already febrile, the heat centre is paralysed and the temperature falls. Why it does not again rise is not clear, and doubtless there are other physiological effects apart from that on temperature which follow the injection of colloids in the infected subject. In any case, we now know that focal reactions are not produced by the specific antigen only. In chronic gonococcal infections precisely similar focal reactions can be induced by other antigens than the gonococcal, and by still less specific agents such as casein or milk. Similar considerations apply to the

treatment of rheumatoid arthritis by injection of non-specific proteins.

We have no precise knowledge of the actual mechanism of these focal reactions in the infected subject, though many hypotheses have been put forward. It is generally believed that the ultimate effect in any case is to produce a greater flow of blood through any indolent inflammatory foci that may be present, with the result that the normal cellular and humoral defences are allowed to come into play. Possibly it accomplishes for the unseen indolent lesion what the surgeon's bistoury does for the visible carbuncle.

Non-specific protein therapy has really a very long history if all the phenomena provisionally assigned to this category do rightly belong to it. We have the mutual interaction of concurrent infections with the ousting of the more chronic by the more acute as evidenced by observations on erysipelas supervening on more chronic processes. The use of Coley's fluid was an attempt to apply this principle to the treatment of sarcoma. The experimental induction of malaria for the amelioration or cure of general paralysis is another instance of prolonged and repeated protein shock therapy. So also is the Schiötz treatment for diphtheria carriers which would seem to depend for any attendant success on the inflammatory reaction produced by the staphylococci sprayed on the throat. Many other phenomena, such as the occasional dramatic effect of normal horse serum in septicaemias, the use of auto-serotherapy and of multiple bleedings, come probably into the same category.

I conclude, therefore, that so far as the early effects (euphoria, focal and general reactions, etc.) following an injection of vaccine are concerned, the action is entirely non-specific. There is no warrant for assuming that the organism, a vaccine of which happens to give a focal reaction in a particular case, is etiologically related to the case. One bacterial colloid can be more potent than another in the production of immediate physiological effects.

In many cases it is the action of the non-specific element of the vaccine that we wish to elicit with a view to cure. This is certainly so in the acute infections and in the more chronic infections (for example, the arthritic) also; we gather that the object now usually aimed at is to produce focal and general reactions by repeated administration of non-specific substances in appropriate dose.

Vaccine therapy, however, as ordinarily practised, involves the repeated injection of a vaccine with a view, not only to cure of an existing infection, but also to prevention of subsequent infection, and here vaccine therapy and vaccine prophylaxis meet on common ground.

Theoretically, therefore, as in ordinary vaccine prophylaxis, specificity of antigen must, at least in our present state of knowledge, be the highest possible if we are to expect the best results. The difficulty arises in preparing a vaccine that can be regarded as specific in many of the affections for which vaccines are used. Valuable information on this point may be expected from those recently organized attempts to control the prevalence of respiratory affections in boarding-schools and institutions by prophylactic vaccines. It is greatly to be hoped that these efforts will be so directed that comparative knowledge may be gained on many important particulars—such, for example, as the qualitative and quantitative vaccine formulae.

SUMMARY.

To sum up briefly what I have put before you, I have emphasized the importance of the non-specific element in vaccine therapy in its purely curative aspect, without ignoring the possible benefits that may accrue from repeated vaccine administration with a view to prophylaxis. I should like to say, however, that in giving my impressions of the rationale of vaccine therapy I have merely been elaborating views that have long been entertained by immunologists but have, I believe, not been adequately ventilated among those who daily practise the method. My object has been achieved if what I have said may help the practitioner to view his aims and achievements in vaccine therapy from a somewhat less conventional angle.

ON THE CONTROL OF HEART DISEASE IN CHILDHOOD.

BY

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ONE of the most serious issues presented to practical medicine to-day is the problem of cardiac disease in the young. By the estimate of Dr. Carey Coombs¹ the onset of two-thirds of our adult cardiac morbidity occurs during the period of life from 5 to 15 years of age. Dr. Askins states that we are losing 18,962 lives per annum from this cause alone, and there must not be forgotten in this connexion "long periods of illness, the misery of repeated breakdowns, and the immense industrial loss involved during the years which elapse between the time when the patient develops the disease and when he is ultimately killed by it,"² if we are to gain an idea of the magnitude of the problem involved.

It is now generally admitted that carditis in childhood is for all practical purposes a rheumatic manifestation; the problem of carditis is thus synonymous with the problem of rheumatism, and in practice the control of heart disease in childhood means the control of the rheumatic child. For this outlook on the question the British Medical Association is in no small measure responsible, and from the illuminating discussions of the whole question arranged by its Sections of Medicine, Diseases of Children, and Public Health in 1923 and 1925, a very considerable body of information has emerged relating to the manifestations of the disease itself and the available agencies for coping with it. A consideration of these discussions brings out clearly that rheumatism is an exceedingly long-drawn-out and chronic infection, which in all its forms should be considered as passing through three stages—the acute, the convalescent, and the quiescent. To be effective, therefore, any attempt at control of the disease must take cognizance of each of these, and be directed along three definite lines.

1. The Acute Stage.

That a very significant diminution in the incidence of carditis can apparently result from efficient handling of this stage has recently been brought out by Dr. Bertram³ in a survey of the after-history of cases treated at the Royal Hospital for Sick Children, Glasgow. She showed that whereas only 24 per cent. of those treated in hospital for their first attack of acute rheumatism or chorea subsequently developed carditis, this sequel occurred in 88 per cent. of those who were treated at home. This is the stage most easily reached by our present organization, and there seems no valid reason why the children's hospitals and the children's departments of the general hospitals at present existent could not satisfactorily cope with it so long as provision can be made to ensure a sufficient length of residence.

2. The Convalescent Stage.

Upon a satisfactory convalescence depends the child's chance of recovery from rheumatic fever or chorea without damage to his heart. The two essentials are: an adequate period of rest and a graduated return to ordinary conditions of living. Treatment of this stage of the disease, therefore, entails the adequate provision of convalescent homes or rest hospitals in sunny and dry areas, where children can receive medical supervision, graduated exercise, and suitable education.

3. The Quiescent Stage.

After the acute and convalescent stages have passed there is a further phase of the disease, extending over many years, and during which the possibilities of recurrences are always present. The very essence of the rheumatic infection is its chronicity and great tendency to relapse, and this third stage, which may be called the "quiescent stage," since no active manifestations are present, is of the greatest significance in any scheme for prevention. It will be readily understood that it is neither feasible nor desirable that this period should be passed in