A British Medical Association Lecture ON IMMUNIZATION AGAINST DIPHTHERIA, SCARLET FEVER, AND MEASLES.*

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BY

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DIPHTHERIA.

THE outcome of Behring's researches on diphtheria, resulting in the introduction of antitoxin, constituted a great advance in the treatment of this disease, by affording the possibility of mitigating and even of aborting attack, provided that the antitoxin is employed at a sufficiently early stage. Moreover, if "contacts" are inoculated before any symptoms have developed, incidence of the disease can be prevented. Unfortunately, however, the passive immunity thus produced is of a very fleeting nature, not extending, as a rule, for a period longer than three weeks or so. Consequently, although of undoubted service in face of an existing outbreak, the inoculated individual will, in all probability, prove just as liable to contract the disease if subsequently exposed to infection.

It is to the work of Schick, first published in 1910, that we owe the introduction of a means of testing for the presence or absence of immunity, and of the method of *active* immunization against diphtheria, which has put into our hands a means of prevention the value of which has now received recognition throughout the civilized world. In this country work on the lines laid down by Schick was not taken up to any extent for a number of years subsequent to its publication. But in America the case was very different, more especially in New York, where, owing to the enthusiasm of Dr. W. M. Park and of his assistants, Drs. Anna Williams and Abraham Zingher, investigations were initiated at an early date and on an extensive scale.

It was not, however, until 1921, on the occasion of an outbreak of virulent diphtheria in the Southmead Infirmary of the Bristol Union, into the circumstances of which I made inquiry, that official investigation into the potential value of the Schick test and of toxin-antitoxin inoculations in connexion with diphtheria prophylaxis was initiated. Here our first attempt at immunization (on a nurse in one of the diphtheria wards, who, unfortunately, turned out to be a serum reactor) was followed by considerable rise of temperature and malaise on the part of the patient. Happily, however, this case proved to be quite exceptional, and, moreover, we subsequently found that by commencing with a minimal preliminary sensitizing dose of the immunizing mixture the full dose could be given twenty-four hours later, even to adults, in whom reaction is usually more marked than in children, without any similar trouble arising.

An account of what was eventually accomplished at the Southmead Infirmary was set out in the "Report on Diphtheria," published by the Ministry of Health. Suffice it to say that since the work was carried out diphtheria has not again been a source of trouble in the infirmary.

The Schick test is a clinical test by means of which the antitoxic immunity of individuals, and consequently their susceptibility or otherwise to the disease, can be judged by a local skin reaction. Experience has shown that the blood of persons who have recovered from diphtheria, or are otherwise immune to the disease, contains not less than 1/30 unit of antitoxin per cubic centimetre. The amount of toxin used in the Schick test is such as will cause a positive reaction in persons with less than this amount of antitoxin in the blood. The test is carried out by injecting into, but not under, the skin of the flexor surface of the forearm 0.2 c.cm. of a freshly made dilution of standardized diphtheria toxin of full strength. Care must be taken that the needle is inserted into the proper layer of the skin, and in this and other minutiae a certain amount of practice is necessary. As a control, a similar amount of the same

solution, previously heated so as to destroy the toxin, is also injected intradermally on the opposite arm. The results first become apparent after about twenty-four hours, but it is difficult to be certain of an accurate reading before at least ninety-six hours have elapsed.

The reaction appears on the surface of the skin at the site of injection as a positive, a negative, a pseudo, or a combined (positive) reaction.

(a) The positive (susceptible) reaction is indicated by a roughly circular area of a more or less deep red colour around the site of injection, while no change occurs on the control arm. It is due to the irritant effect of the toxin acting upon tissue cells which are not protected by antitoxin. A positive reaction indicates that little or no antitoxin is present in the patient's blood, and that, in consequence, susceptibility to diphtheria exists.

(b) In the negative (immune) reaction there is no change at the site of injection on either arm, and a result of this kind indicates immunity from diphtheria.

(c) In a "pseudo" reaction there is an approximately equal area of redness on both arms, which usually reaches its height in about twenty-four hours, and may have completely faded by the fourth day. The pseudo reaction is non-specific, and occurs in persons susceptible to the action of "foreign" proteins in general; it is to be regarded, equally with the negative reaction, as indicating immunity to diphtheria.

(d) The combined (positive) reaction presents elements of both the positive and the pseudo reaction in the same individual. In this case a reaction occurs in both arms, that on the arm inoculated with potent toxin being larger and usually presenting a distinctly defined, central red area. The pseudo element on both arms disappears early, leaving persistent evidence of the true positive reaction.

Under the auspices of the Ministry of Health Schick-testing, followed by immunization of individuals giving a positive reaction to the test, has now been carried out on about 50,000 children and adults in various "centres," institutions, and secondary schools in this country, with the satisfactory result that, with the exception of two or three specially susceptible cases, none of these children, even when exposed to risk of infection, has subsequently contracted the disease. And whereas, in one of these institutions, limited outbreaks of diphtheria had, for several years, been the cause of much trouble and expense at intervals of a few months only, since the work was completed—with the added precaution of the immunization, when requisite, of further admissions—there has been absolutely no recrudescence of the disease.

In view of the increasing prevalence of diphtheria the suggestion has been made that the education authorities should follow the lead of New York and undertake the testing and immunization by the Schick method of all children of school age. But I would suggest that it is of even more importance to aim at immunization of all children of pre-school age—at the period, that is, of greatest danger, and in order to obviate appreciable risk of contracting the disease when they come in close contact with other children on joining school. This work, until recently, had only been attempted on a comparatively insignificant scale in this country.

Doubtless publication of reports (unfortunately justified) as to certain fatalities which occurred in Austria about a couple of years ago; in some similar instances at a previous date in America, in consequence of the use, for immunization purposes, of batches of toxin-antitoxin mixture subsequently found to contain excess of toxin; and, most recently, in Bunderberg, Queensland, concerning which an authoritative report is still awaited, has somewhat naturally deterred various authorities from advocating and arranging facilities for carrying out the work. However, recurrence of such mishaps is improbable in future, owing to the fact that anatoxin, or toxoid, which is entirely non-poisonous, is now successfully replacing toxin in the immunizing mixture.

In view of the fact that a high percentage of infants over the age of 6 months are likely to be susceptible considerable saving of time and energy can be gained by omission of the preliminary Schick test. Research, moreover, is being directed to the possibility of reducing the

* This is an abridgement of the lecture, which was illustrated with lantern slides in natural colour photography.

three immunizing doses now required to two, or even one, and also of combining a first immunizing dose with the preliminary test. But, whenever possible, it is most desirable to perform a further Schick test about three months subsequent to the last immunizing inoculation, as it is known that in a few instances the ordinary procedure may not suffice for conferring adequate protection, and so may have to be repeated.

Reduction in the number of inoculations requisite for the attainment of an adequate degree of protection would undoubtedly constitute a valuable advance towards more general acceptance of the method. But even so, opposition is still likely to be encountered, as there undoubtedly exists widespread objection to the adoption of any therapeutic measures involving the use of inoculation methods. Yet it is certain that we have at our disposal, in the immunization of infants and those of school age, a most powerful weapon in our fight against the ravages of diphtheria, but much propaganda work will be essential in this country if the desired end is ever to be attained.

I desire also to advocate most strongly the Schick-testing and, if necessary, the immunization of all nurses employed in fever hospitals before being allowed on duty in diphtheria wards. This, I am glad to know, has been the rule as regards the staff of the Bristol City Hospital, for instance, since January, 1922, with the result that no completely immunized member of the staff has ever developed clinical diphtheria. But, as pointed out by Sir George Newman, "there are still many infectious diseases hospitals where nurses are allowed to attend diphtheria cases without having been offered the advantage of this method of protection." He adds that "one large authority calculated that the total cost to the hospital of every nurse who took diphtheria was £28 10s., while the cost of immunizing a nurse was 2s. 9d. only."

SCARLET FEVER.

During an official visit to New York a few years ago I was afforded opportunity of studying work then in progress on the bacteriology of scarlet fever, on methods of immunization, and on the specific treatment of individuals who had already contracted the disease. The work was, in large measure, concerned with what is known as the "Dick test," so named after its introducers, a test which exhibits many analogies to the "Schick test" for diphtheria.

As the outcome of their study of the bacteriology of scarlet fever the Dicks, apparently confirming earlier results by Klein, Tunnicliffe, Bliss, and Mervyn Gordon, claim that a haemolytic streptococcus, long recognized as a micro-organism constantly present in the nasopharyngeal cavities of patients suffering from scarlet fever, constitutes the probable etiological agent of the disease. But considerable difficulty has been experienced by all who have worked at the subject, owing to the fact that it seemed practically impossible, by the inoculation of the usual laboratory animals, to produce a disease bearing any definite resemblance to scarlet fever. Various observers have shown, however, that by cultivation of the supposedly specific haemolytic streptococcus in blood-broth a toxin can readily be produced inoculation of which in the human subject is said to have caused some of the main features of the natural disease, including the rash. This toxin, suitably diluted, is used for the purpose of the Dick test for determination of the susceptibility or otherwise of individuals to scarlet fever, the test fluid being inoculated intradermally in precisely the same manner as the solution of diphtheria toxin in performance of the Schick test. The results following on the use of this test are also very similar to those observed in the case of the Schick test, except that the reactions appear more rapidly, being at their maximum intensity after an interval of about twenty-four hours, and subsequently fade more quickly.

Further evidence in favour of possible specificity of the toxin is afforded by the fact that its effects can be completely neutralized by admixture with blood serum obtained from a convalescent scarlet fever patient, or with the serum of a horse which has been immunized with the toxin. Furthermore, if serum from either of these sources be injected intradermally into the skin of a patient suffering

from an early scarlet fever rash a blanching of the rash over the area of the injection is produced in the course of six to eight hours subsequently. This phenomenon, of considerable service as an aid in diagnosis, is known as the Schultz-Charlton reaction.

As regards the extent of the reaction following on the Dick test among children not suffering from scarlet fever very similar results to those well known in connexion with the Schick test have been obtained. Thus in the earliest stage of life a child apparently obtains fleeting placental immunity from the mother, so that up to the age of 3 months, at any rate, the Dick test is likely to afford a negative result. At subsequent ages the relative proportion of positive and negative results, as in the case of the Schick test, will develop according to age, to social status, and as to whether the child is town or country bred.

Many thousands of children in hospitals or infant welfare centres in New York, found to give a positive reaction to the Dick test, have now been inoculated intramuscularly with scarlatinal haemolytic streptococcus toxin. As in the case of the Schick work, these inoculations have usually been three in number at weekly intervals. These, in the majority of instances, have not given rise to any undue reaction locally or constitutionally. Again, as in the case of the Schick work, it is important that the results of these inoculations *qua* immunization should be determined by a further Dick test after an interval of three or four months from the last inoculation.

About a couple of years ago the Committee on Scarlet Fever, appointed by the Ministry of Health, decided that it was desirable that intensive investigation into the etiological relationship of certain haemolytic streptococci to this disease, and the diagnostic value of the Dick test, should be undertaken under the co-ordinated direction of a team of expert pathologists and clinicians. With the object of ensuring, as far as possible, that the work carried out in the different laboratories should be on strictly comparable lines it was arranged that similar methods and, so far as possible, identical materials should be employed by all the different workers concerned.

The scheme ultimately adopted has comprised, on the clinical side, performance of the Dick test as a routine measure on all patients notified as suffering from scarlet fever admitted to certain infectious diseases hospitals, together with a further Dick test, when possible, prior to their discharge. On the pathological side, throat discharges of scarlet fever patients admitted to these hospitals have been examined for the presence of haemolytic streptococci, while, for purposes of comparison and control, strains of these micro-organisms of non-scarlatinal origin have also been isolated from various sources, and submitted to thorough investigation in the various laboratories concerned.

It is essential to bear in mind that the problems connected with the diagnosis of scarlet fever, and of immunization against this disease, are, in certain respects at any rate, much more complex than in the case of similar work in connexion with diphtheria. Of primary importance is the necessity for accurate differentiation of the specific micro-organisms responsible for the production of the disease in susceptible individuals. The departmental sub-committee has lately arrived at the conclusion that a haemolytic streptococcus is to be regarded as the responsible agent; but the variety of strains that have been isolated from the throats of patients suffering from this disease renders it difficult, as yet, to determine precisely whether one particular strain, or any of several varying strains, are specially concerned. Again, the divergent results not infrequently met with in connexion with the classification of haemolytic streptococci by agglutination and absorption tests introduce further difficulties.

An interesting point, to which sufficient attention has hardly perhaps hitherto been paid, concerns the nature of the population which it is sought to immunize *qua* degree of susceptibility as estimated by means of the intradermal test. Experience has clearly indicated, in the case of our work on diphtheria, that where a certain general basis of immunity already exists it is comparatively easy to increase the extent of this immunity to a sufficiently high level. On the other hand, in certain

institutions which for years previously had been completely free from this disease, probably owing to the fact that most of the children are recruited from unaffected rural districts, we found that immunity was practically non-existent. And so, unfortunately, the building up of a sufficient degree of immunity proved a matter of no little difficulty, requiring indeed, as eventually became evident, a time interval more lengthy than previously observed. It remains to be seen whether the response to immunization work in scarlet fever will be found to run on similar lines. It is, I think, as yet hardly possible to estimate what may eventually prove to be its precise value as compared with immunization against diphtheria. As a matter of fact, so far as is at present known, attainment of anything like complete immunity by means of inoculation methods appears to be decidedly more difficult of accomplishment in scarlet fever than is the case with diphtheria. Moreover, there is, unfortunately, reason for believing that immunity thus produced is by no means permanent.

MEASLES.

As in diphtheria and scarlet fever, so also in the case of measles, infants appear to inherit some temporary immunity from their mothers, which is said to last until the fifth or sixth month of extrauterine life. From this period onwards, however, up to the age of 5 years, mortality from measles is high (from 13 to 15 per cent.), mainly owing to its complications—a fact which renders desirable some more effective method than “the careful nursing of each case” which at present, as we are told, constitutes “the only possible way of reducing its mortality.” It is therefore of interest to realize that a method of immunization has been worked out recently which has been reported by many observers to be of value in this connexion. The method consists, in its original form, of the subcutaneous administration of small doses of serum obtained from patients recently convalescent from the disease. If required, advantage may be taken of the fact that antibodies are also present, although in smaller quantity, in the serum of adults who have had measles.

It is of interest to note that as long ago as the year 1758 Francis Home of Edinburgh introduced a method of active immunization against measles which had been suggested by Alexander Monro in the previous year. About forty years ago Hugh Thompson, a vaccinator appointed by the Faculty of Physicians and Surgeons of Glasgow, devised a method of blistering measles convalescents and vaccinating contacts with the serum, for which he claimed good results. In this connexion, as in so many others, it is curious to note how history has a habit of repeating itself, as illustrated by the fact that only last year Professor Karl Leiner of Vienna introduced a similar method, the employment of which, however, he discontinued in consequence of a campaign of opposition from the daily press.

As in the case of scarlet fever, progress in regard to immunization against measles has been greatly hampered owing to want of knowledge as regards the specific virus of measles, although various micro-organisms have been incriminated from time to time. But, pending more definite knowledge as to the bacteriology of measles, the method of immunization by means of “convalescent serum” to which I have already referred is obviously one which demands our serious consideration. This was first employed by Nicolle and Conseil during a small epidemic of measles in Tunis in 1916, and has subsequently been employed extensively by Park and Zingher and by Richardson and Connor in America, by Degkwitz in Munich, and by Debré in Paris. Various workers have since modified the original methods of Nicolle and Conseil, and the production of active immunity has been attempted, apparently with some measure of success.

To achieve passive immunity the following methods of employing the serum are feasible: (1) Injection of convalescent serum into healthy contacts; in this case an immunity which lasts about a month is produced. (2) Injection during the first five or six days of the incubation period, when, as Degkwitz and others have shown, the patient will not develop measles; although the later it is injected the larger will have to be the dose.

If the serum be injected *after the sixth and before the ninth day*, measles will, nevertheless, develop; but the attack will be modified in the length of its invasion period, and by the absence of catarrhal symptoms, Koplik spots, and high temperature. The eruption also, if present, is less confluent, and the macules are smaller.

Injection at the beginning of the period of invasion (about the tenth day) will result only in *local* inhibition of the rash—the phenomenon of Debré—as regards which it should perhaps be mentioned that it is not, as has been suggested, comparable with the Schultz-Charlton reaction in scarlet fever.

With regard to the production of *active* immunity, besides the method mentioned of inducing a modified attack, Nicolle has suggested that the child it is desired to protect be given 10 c.cm. of convalescent serum, and, twenty-four hours later, 1 c.cm. of blood from an early case of measles. If the injection of blood be repeated, it is stated that the immunity produced is likely to be permanent. This method is probably reproduced in Nature when serum is given to a very early case.

The results obtained by the majority of workers who have used the earlier methods referred to have been decidedly favourable, as, indeed, is evidenced by the fact that municipal collecting and distributing centres for the serum have been established in connexion with hospitals in Germany, France, and America.

No original work on the subject had been published in this country prior to a paper by Dr. W. S. C. Copeman,¹ recording successful results obtained by him in face of a somewhat exceptionally severe epidemic of the disease which prevailed during the period February to July, 1925, at the Children's Hospital in Paris; and it will be of interest to members of the Harrogate Division to recall the fact that Drs. Smith and Miller, working on similar lines, recorded some successful results in a communication to the Pathological Society of Great Britain and Ireland in January, 1927.

In view of the importance of lessening, if possible, the mortality from measles in this country, we shall doubtless all agree that it is eminently desirable that investigation of the whole subject should be officially undertaken as speedily as possible, perhaps somewhat on the lines of that recently initiated in connexion with the work of the departmental committee on scarlet fever.

Meanwhile, it is encouraging to learn from Sir George Newman that the Ministry of Health, in conjunction with the Medical Research Council, is maintaining close observation upon the important investigations of Dr. Degkwitz, especially concerning the use of a sheep serum introduced by him, and the prophylaxis of measles generally.

REFERENCE.

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FUNGUS INFECTIONS OF THE HANDS AND FEET.

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THE diseases to which I wish to draw attention are deeply situated in the epidermis and are very refractory to treatment. Many varieties of fungi may be pathogenic and provoke changes in the skin. Their classification is complicated, but broadly they may be divided into (1) the ringworms (*Gymnosaceae*), (2) the yeasts (*Saccharomyces*), and (3) some members of the order *Hyphomycetes* such as *monilia*. The reactions of the skin may be to all appearances identical, and the same species of fungus is able to produce lesions which differ clinically. The subject is still further complicated because many moulds and fungi are saprophytic, occurring on normal skin without producing any reaction, but both the yeasts and the ringworm *mycelia* have been found consistently invading the layers of the epidermis in the same type of skin lesion; in addition, the lesions have also been produced successfully by rubbing