PREVENTION AND CONTROL OF MEASLES, SCARLET FEVER, AND DIPHTHERIA IN INSTITUTIONS AND THE HOME *

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We do not intend to include in the present survey any account of the methods of isolation now practised, as these fall rather into the realms of public health. We are now concerned with the recent advances in the preventive measures at our disposal for dealing with diphtheria, scarlet fever, and measles.

DIPHTHERIA

The greatest advance in our knowledge of this disease came with the introduction of the Schick test. This consists of the intradermic inoculation of diphtheria exotoxin so diluted that the 0.2 c.cm. injected contains 1/50 of a minimum dose lethal to a guinea-pig of 250 grams weight (M.L.D.). Heated toxin of similar strength is used as a control. As a result of this dose, which was first recommended by Schick, and has been adhered to by most workers, the community can be divided into several distinct classes.

1. *Negative Reaction.*—All negative reactors have been shown to have at least 1/40 of a unit of diphtheria antitoxin per c.cm. of blood serum. This is sufficient protection against a normal infecting dose of diphtheria bacilli.

2. *Positive Reaction.*—When there is less than 1/40 of a unit per c.cm. a red, raised erythematous patch appears in about twenty-four hours, is best seen at three days, and persists for a week, when a branny desquamation appears with a brown discoloration of the area. Occasionally a typical positive reaction is seen within twenty-four hours and disappears before three days. These are probably border-line cases whose blood has about 1/40 of a unit per c.cm., and it will later be shown that these do not need to be immunized. The control injection in these two reactions is quite negative throughout.

3. *Pseudo-Negative.*—In this type of reaction there is an exactly similar response to the control and to the unheated toxin. The reaction disappears within forty-eight hours and is probably due to a sensitivity to the protein in the inoculum. These are immunes.

4. *Pseudo-Combined Positive.*—Both this and the previous type of reaction occur more commonly in convalescents from diphtheria, in carriers, and in people who have been immunized. In this type both the control and the test inoculations react positively. The test, however, gives a much larger reaction, consisting as it does of a protein reaction, equivalent to the control injection, plus a reaction to the toxin.* The protein reaction fades rapidly in both injections, leaving a normal positive reading in the test. It is chiefly on account of these reactions that it is essential to read the Schick test at least on two separate occasions, that is, after twenty-four hours, and three days, and if there remains any doubt, again at the end of the week. One is well advised to follow the rule laid down by Dudley¹—to immunize all those who give doubtful reactions as well as the definitely positive, as diphtheria occurring in an individual who has been told he is immune is apt to cause prejudice against the methods used.

* Read in opening a discussion in the Section of Diseases of Children at the Annual Meeting of the British Medical Association, Eastbourne, 1931.

About 85 per cent. of infants up to 6 months are Schick-immune (equivalent to the adult female Schick-negative rate). Thereafter, up to 5 years of age comes the "diphtheria period," when 90 per cent. are susceptible. The infants have a passive immunity transferred by the placenta and greatly increased by the colostrum (which has a higher concentration of antitoxin than the blood) and later by the milk. This passive immunity can be prolonged by continued breast-feeding. As soon as this passive immunity is lost the children, losing their circulating antitoxin, become Schick-positive. As they approach the adult stage more and more people react negatively. This is out of all proportion to the diphtheria case rate. Therefore, it is not due to immunization by a previous attack of diphtheria, but is, in all probability, due to subminimal repeated infections causing a latent immunization. It has been shown that in isolated communities where there has been no diphtheria for many years the Schick-positive rate is inordinately high, whereas in similar communities where there have been repeated outbreaks of diphtheria the Schick-positives form a very low proportion. There is no doubt that repeated encounters with the bacillus are sufficient to produce a degree of immunity equivalent to the Schick-immune, and in all probability we have to be thankful for the 3 per cent. of the normal population who are virulent carriers for most of our immunity. This immunity may be complete or incomplete. In the latter case we have the "Schick-positive immunes" of Glenny, who has demonstrated the enormous difference between primary and secondary stimulation. On the very first meeting with an antigen (in this case we refer to diphtheria toxin either in the form of prophylactic or the Klebs-Loeffler bacillus itself) the antibody response of the individual takes a short while to show itself, is never very marked, and rapidly falls. On a second meeting, however, the response is almost immediate, is very great, and remains at a permanently high level. The practical value of this observation is enormous. In the first place, it probably explains why about 50 per cent. of diphtheria convalescents are still Schick-positive. They had probably never been in contact with the K.L.B. before, and were therefore Schick-positive and developed, perhaps, severe diphtheria. Their antitoxin rose during the attack, only to fall below 1/40 per c.cm. afterwards. It is significant, however, that very few of them indeed are subject to a second attack; this is readily explained by the fact that the mere coming in contact with the organism a second time is sufficient to shoot their antitoxin titre so high as to give them a good immunity. The observation receives its practical application in routine Schick-testing and immunization, as it is claimed to be unnecessary to immunize those convalescents who are Schick-positive. This is not a safe rule to follow without having the titre of the blood antitoxin estimated, because there is a small group of people who are naturally bad antitoxin producers; this tendency appears to be familial, inasmuch as if a child acquires the same blood group as a poor antitoxin-producing father he will probably inherit the defect; whereas were he to follow the mother's group or be of another group he would follow the ordinary laws of the Schick reaction in the population. This hereditary genetic defect of Hirschfeld² is not linked to any particular blood group.

Active Immunization

Many means of artificial immunization have been recommended, and since the introduction of the Schick reaction it has been possible to estimate the relative merits of the methods. To do this it is essential to Schick-test before commencing immunization and also at intervals

also to swab the staff at regular intervals, particularly after an outbreak of diphtheria.

In all institutions where a long stay is contemplated the children as well as the staff should be actively immunized. In hospital this is not possible, but we can still admit new patients to an infected ward by Schick-testing and, if necessary, giving a passive immunity.

No immunization measure alone is of value in an epidemic; the only certain method is carrier control, both of convalescent and of contact carriers.

In *private and public health* work we cannot urge too strongly that as many children as possible, after the age of 1 year, should be Schick-tested and actively immunized until they are immune, preferably using T.A.M. or T.A.F.

SCARLET FEVER

A specific haemolytic streptococcus is now identified as the causal agent of scarlet fever. It cannot be isolated from the blood in the early stages of the fever (except in fulminating cases), because the symptoms are those of a toxæmia, and it is not till later, when the septic complications occur, that the organisms can be at all readily obtained from lesions. The toxins of the streptococcus when injected in a dose of 0.1 c.cm. *intramuscularly* will produce a typical scarlet fever rash in about 7 per cent. of children; whereas if a dose of 1 or 2 c.cm. is used, all children injected will develop the rash. A similar rash can be obtained with a few other strains of haemolytic streptococci, but much larger doses are required.

The Dick Test

In the Dick test 0.2 c.cm. of a 1/1,000 dilution of the specific toxin is injected intradermally into the skin of the forearm, and a similar amount of toxin, heated to 100° C. for half an hour, is used as a control. A positive reaction is indicated by an erythematous area in the test arm, which appears within twelve hours, reaches its maximum in twenty-four hours, and then rapidly disappears. Pseudo-reactions do not occur in children, and are much rarer in adults than the pseudo-Schick reactions. Care must be taken not to inject too deeply, as the toxin will be readily absorbed and may give a false negative. This Dick test is a toxin-antitoxin reaction in the skin; the injected toxin being neutralized if there is sufficient circulating antitoxin.

It is said that children up to 6 months inherit an immunity from the mothers, but this is now challenged because their blood does not always cause blanching of a scarlet fever rash, and it has been suggested⁸ that many of them do not react because of the general non-reactivity of the infantile tissues to streptococci. They lose this passive immunity or non-reactivity at about 6 months, and thereafter the majority are Dick-positive, slowly becoming negative in adult life. This alteration in the reaction, as in diphtheria, is probably due to repeated subinfections with the haemolytic streptococcus which is kept among us by carriers, both contact and convalescent. Treatment of scarlet fever carriers has not yet reached the stage attained in diphtheria, but in any institution with recurrent epidemics of scarlet fever it is advisable to take routine throat swabs, and isolate any persons who have haemolytic streptococci in their throats. It has also been suggested⁹ that the complement fixation test is a useful means of isolating carriers, as they react positively, as do also 98 per cent. of scarlet fever cases from the second to the fifth weeks.

In *early cases* of scarlet fever only about 40 per cent. of patients are Dick-positive. This curious state of affairs is explained as follows:

(a) The skin has a diminished reactivity to all toxins in the early stages of an acute infectious disease. Both in

scarlet fever and measles there is a lessened reactivity to tuberculin, streptococcus toxins, etc.

(b) The rash having already appeared as the result of the toxæmia, the skin is not so sensitive to further doses of toxin.

(c) It will be recalled that in the Schick test of a carrier it was emphasized that the reaction of a Schick-positive could be readily converted by a few bacilli in the throat acting as a secondary stimulus. In like manner the infection, if only for twenty-four hours, with the streptococcus may readily turn the Dick reaction negative. It can readily be seen that although it is advocated in diagnosis of an early scarlet fever rash, the Dick test is in itself insufficient evidence either way.

In *convalescents* 10 to 15 per cent. remain Dick-positive. There are various factors concerned in this persistence of the positive reaction.

1. Toyada¹⁰ has split up the streptococcus toxin into exotoxin (heat-labile) and endotoxin (heat-stable). Of this 15 per cent., he found that 13 per cent. reacted *only* to the endotoxin factor and their bloods gave a good blanching reaction (Schultz-Charlton) when injected into a scarlet fever rash. They are immune. The other 2 per cent. gave reactions to both endotoxin and exotoxin and they gave weak blanching reactions. These are only partially immune, but a secondary stimulus would rapidly convert them into negative reactors. He holds that the endotoxic reaction merely indicates previous experience with the streptococcus and a partial immunity. He, therefore, advocates using only the heat-labile exotoxin both in the Dick test and in immunization.

2. Convalescents from scarlet fever who have been treated early in the disease with concentrated antitoxin show a much higher rate of Dick-positives (30 to 40 per cent.) than do other convalescents.¹¹ This would apparently indicate that the disease is fought "passively" and that the patient has no opportunity to produce his own active immunity which would be permanent.

3. Of the four serological groups of scarlet fever streptococci, it has been demonstrated¹² that many more patients remain Dick-positive after infection with Group 4 than with any other group, and least of all with Group 2. This suggests that Group 2 of the *Streptococcus scarlatinae* is most highly toxigenic and Group 4 least so. Finally, in cases of relapse it has occasionally been observed¹³ that the infecting strain in the relapse is different from that in the primary attack. This would indicate that if a patient remains Dick-positive after an attack of scarlet fever with Group 4, he may become infected from another patient in the ward with a different serological strain.

Immunization in Scarlet Fever

Passive Immunity.—In an epidemic of scarlet fever, active immunization is obviously of no avail. We now have available a purified concentrated antitoxin serum which can be used both therapeutically (in severe toxæmic cases) and prophylactically. A small dose, 5 c.cm. intramuscularly, will turn a Dick-positive reactor negative within twenty-four hours, and this passive immunity will last two to three weeks. In hospital and institutional practice this has been a great boon. When a case of scarlet fever is reported in a ward all the inmates should be Dick-tested immediately. The results are read next day and serum is given to all positive and doubtful reactors at once, that is, twenty-four hours after the first rash appeared. The enormous success attendant upon the adoption of this routine can be attributed to the rapidity of the diagnostic reaction, as the whole procedure falls well within the incubation period for scarlet fever.

Active Immunity.—Small doses of toxin are injected at weekly intervals until at least 20,000 skin test doses have been administered. Our practice has been to inject 0.1 c.cm. scarlet fever prophylactic A (Burroughs Wellcome and Co.) intramuscularly. If there is no reaction within

three days the following doses are injected at weekly intervals: 0.4 c.cm.A, 1 c.cm.A, 0.25 c.cm.C, 0.5 c.cm.C, 1.0 c.cm.C, the total being equivalent to 38,500 skin test doses (prophylactic A contains 2,500 skin test doses per c.cm. and prophylactic C 20,000). Reactions, in the form of sore arm and malaise, occur but rarely and are not severe. Occasionally, however, a scarlatiniform reaction occurs. This takes the form of a toxæmia, the patient developing a scarlet fever rash, sore throat, and rise of temperature for twenty-four to forty-eight hours. All this rapidly subsides and none of the complications of scarlet fever ever occur because these are septicaemic and the reaction here is only toxæmic. The patient has now developed a high degree of active immunity and does not need further injections. The reaction is uncommon in adults (2 in 270 nurses immunized) but is said to occur in about 7 per cent. of children.¹⁴ Immunity after the normal course of injections is usually complete within one month after the last injection, and is of many years' duration. If there are any signs of the Dick test again becoming positive another injection is usually all that is necessary.

Institutional Practice.—All staff should be Dick-tested and, if positive, actively immunized on entry. Similar measures should be adopted in public schools and other institutions where the children are resident for long periods. In an epidemic, the whole population should be Dick-tested and serum given immediately. By this means no second case of scarlet fever has occurred in our hospital for three and a half years. The isolation of *carriers* of haemolytic streptococci is a measure which we would urge in cases of repeated epidemics, as they will readily infect the patients as soon as the effects of the prophylactic serum have worn off, in about three weeks. Our wards are now not closed for scarlet fever, as all new admissions for ten days after a notified case are Dick-tested and passively immunized.

We wish here to draw special attention to a measure we have adopted for several years. Streptococcal infections with a rash and sore throat, etc., are fairly common after operations on the throat and nasopharynx. Surgeons are apt to disregard these and not look upon them as true scarlet fever. We have often seen two or three other children in a ward develop typical scarlet fever three days after such a case, and we therefore treat the rest of the ward prophylactically exactly as for a scarlet fever whenever such an infection occurs. Several of the surgeons at Great Ormond Street now have all patients for these operations Dick-tested *beforehand* and serum given where necessary, and have by these means eliminated such scarlatiniform reactions for several years. We would advocate this as a routine measure for all children's wards.

Private and Public Health Practice.—When confronted with contacts of scarlet fever in private practice each case must be treated on its own merits. Obviously if a child is in poor health we should not withhold our prophylaxis, but it is not an ideal state of affairs to have to give a child a dose of horse serum each time it is exposed to scarlet fever. It would be wiser when possible to provide the passive immunity once, and then commence as soon as is practicable a course of injections for active immunization. This would do away with the necessity for repeated serum injections with their attendant risks. In public health work we would advocate that all children who are Schick-tested should at the same time be Dick-tested. Both reactions are read on the first day and the Schick again on the third day. Thereafter the two courses of active immunity can be given concurrently, the two solutions being mixed in the same syringe just before injection. By means of this active immunity the scarlet fever incidence in Dairen has been reduced from 43.3 per 1,000 in 1925, to 1 per 1,000 in 1930.

MEASLES SERUM

With regard to the use of human convalescent serum in the prophylaxis of measles we have not much to add to the paper¹⁵ upon the subject which we read in the Section of Medicine at the Annual Meeting of the Association in Winnipeg last year. Further experience of the method confirms our opinion of the value of the procedure.

Historical

Nicolle and Conseil¹⁶ in 1916 succeeded in protecting children who had been exposed to measles infection by injecting them with convalescent serum. Since then many observers have published similar results, which all agree in establishing the fact that convalescent measles serum is of very great value in prophylaxis when injected in adequate amount shortly after exposure to infection. Debré and Ravina¹⁷ in 1923 suggested the use of convalescent serum to produce a mild attack rather than complete protection, and this would appear to be the more desirable method in many cases, particularly in home as opposed to institutional cases, because the mild attack of measles induced would give the patient an active immunity which is permanent, whereas the immunity produced by a prophylactic dose is passive and lasts only from two to four weeks. Owing to the difficulty in procuring sufficient supplies of human serum for its use on a large scale, it is obvious that as soon as a causal organism for measles is definitely established and an appropriate animal serum prepared, the use of human serum will be suspended. The animal serums at present available are those of Tunncliffe, Degkwitz, and Ferry and Fisher, all of which are prepared from a "green" streptococcus, which is held, though not generally accepted, to be the causal agent of the disease. Gunn,¹⁸ of the Metropolitan Asylums Board, in a comparative survey of these animal serums and human convalescent serum, found that Ferry and Fisher's serum failed to protect, Degkwitz's serum protected 40 per cent., Tunncliffe's serum protected 43 per cent., and human convalescent serum protected 95.7 per cent. of the individuals injected. These results are similar to those obtained by other workers, and show that, at present, human convalescent serum is by far the most reliable. A similar condition obtains in poliomyelitis and encephalitis lethargica, which are virus diseases, and reference may incidentally be made to the observation of Degkwitz¹⁹ on the cultivability of the measles virus, but McCartney²⁰ states that the prophylactic use of Degkwitz's animal serum, presumably made from the virus cultures, has not furnished any evidence that measles-virus immune bodies are present.

Preparation of the Serum

Children are obviously not suitable donors of adequate quantities of blood, so that we have obtained all our supplies from adults, and we have been fortunate in securing the co-operation of Dr. Massingham, of the London Fever Hospital, where many adult cases of measles are treated. Only normal, uncomplicated cases of measles are utilized for this purpose, and the greatest care is taken to exclude the possibility of any other infection, particularly syphilis or tubercle. From seven to fourteen days after deferescence patients are bled aseptically to the extent of 200 to 400 c.cm. into sterile oxalate solution, this procedure yielding as much as 60 per cent. of serum, after precipitation of the oxalate with calcium chloride. Sterility tests and a Wassermann reaction are done on every serum, and if these are satisfactory, 0.5 per cent. phenol is added, and the serum is pooled with several other serums, to ensure as far as possible a uniform potency of the final product. Before it is stored or bottled for use, the serum is filtered through a Seitz bacterial filter, and a final sterility test done.

Effects of Administration

No ill-effects have ever followed the use of a carefully prepared serum, and any untoward results can usually be traced to insufficient care in the preparation. The method of preparation which we have outlined above practically eliminates any possibility of conveying a tuberculous infection with the serum, for Kraus has tested many measles convalescent serums made without the double precautions (phenolizing and filtering) which we adopt, and has never produced tuberculosis in the inoculated guinea-pigs. As the serum is of human origin, anaphylaxis or serum reactions do not occur, and it is unlikely that an attack of asthma or other allergic manifestation will be produced by the serum injections. Different results can be obtained from the use of the serum, depending on the stage of incubation at which the injection is given.

Injected before the fifth or sixth day of incubation, the serum affords complete protection—a passive immunity which lasts from two to four weeks. This Copeman²¹ calls "sero-prevention." Injected on the sixth to the ninth day of incubation, the serum protects only partially, and a very mild attack of measles usually ensues ("sero-attenuation"). Injected after the ninth day no benefit is to be hoped for from the serum, whereas injection on the tenth day produces Debré's phenomenon—a local blanching at the site of the injection.

The attenuated attack gives rise to a permanent active immunity, which is our aim in private practice where the individual himself has alone to be considered, whereas in institutional work it is complete protection which is aimed at. Of course, where a very sick child has been exposed to measles, whether at home or in an institution, it must be protected at all costs, and one would inject the serum as soon as possible, and give a slightly larger dose than the normal for a child of that age. The attenuated attack is usually a very mild affair: a slight bout of fever (100° F.) for a day or two at about the fourteenth day of incubation; others may be apyrexial, with a few measles spots on the trunk or face; others, again, may have a typical attack of measles with coryza and bronchitis, which has all subsided in twenty-four to forty-eight hours. We have never seen Koplik's spots in any of these cases arising after the injection of convalescent serum. Sometimes after a long incubation period—even as much as twenty-six days in some cases—a mild attack of measles may occur, which, from a hospital administration point of view, is rather disturbing, as it holds a ward in quarantine for nearly four weeks. If, however, serum is given to all the new admissions, the quarantine period need not interfere with the normal working of the ward.

Dosage

In order to ensure the production of complete protection, we have recently increased the doses of serum injected to 5 and 7 c.cm. intramuscularly for children under 3 years and over 3 respectively. Whole blood may be used instead of serum, in which case the blood of a convalescent is injected intramuscularly into the recipient, the amount injected being double the serum dose. It has also been suggested that the whole blood or the serum of any healthy adult who has had measles may be used, and this scheme has recently been tried in Birmingham,²² where 146 children have been treated in this way. The results are reported as very satisfactory, 57 children having had attenuated attacks (the result aimed at) and 85 children being fully protected. Serum has been tried in the treatment of severe measles, but without success, as the antibody content is not sufficiently high, and enormous doses would be required to produce any effect. For the same reason the serum is unable to blanch the rash, although it is sufficiently potent to prevent the appearance of the rash

in an area if injected shortly before the general rash appears (Debré's phenomenon).²³

Results

Debré, Gunn, and many others, have reported complete protection in from 80 to 96 per cent. of the cases injected. Our own series now amounts to 625 cases, in which the advocated dose of serum was injected within the first five days of exposure to infection, and a further 46 cases in which either too little serum was injected or an adequate dose was injected between the sixth and ninth days of incubation. Of this total of 671 cases, 518 were injected by us at the Children's Hospital, following ward infections, and 153 cases from practitioners in various parts of the country, following home or hospital infections.

Analysis of Cases Injected

It is impossible to say how many children exposed to infection would develop measles, but Gunn, working at a fever hospital, and with facilities for studying cross-infections, had ample opportunities for controls. His series included uninoculated wards, and wards inoculated with

ANALYSIS OF CASES INJECTED WITH CONVALESCENT MEASLES SERUM

1. Cases at the Hospital for Sick Children, Great Ormond Street.
2. Cases at other hospitals and of private practitioners.

	Injection Made Before 5th Day.	Protection.	Failures.	Injection 6th-9th Day.	Protection.	Attacks.
1	514	507	7 (Attacks mild)	4	0	4 (3 mild 1 severe)
2	111 3‡	106 0	5* 3*	39	26	13†

Total 625, appropriately injected, with 613 cases, = 98.1 per cent., protection.
* In these cases the rash appeared 8 to 21 days after the serum was given and the attacks were all mild or very mild.

† These cases were all mild and the rash appeared in 3 to 10 days after the serum was given. In several of these cases sero-attenuation rather than sero-protection was aimed at.

‡ In these three cases too little serum was injected.

various animal serums and with convalescent serum. His 95.7 per cent., together with our figure of 98.1 per cent., protection affords striking and sufficient proof that, until an efficient animal serum is prepared, convalescent measles serum is the best weapon we have for preventing measles, and it should be more widely used than it is at present.

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