ATTENUATION AND PREVENTION OF MEASLES *

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The subject which has been chosen for discussion to-day is ripe for consideration on practical lines. On the one hand we have a disease responsible for a large loss of life and much permanent disability among that section of the population that has been the subject of special solicitude from public health authorities. On the other hand research promises that if certain difficulties can be overcome the ravages of measles might be greatly curtailed.

We have been in possession of the requisite knowledge for several years, yet very little effort has been made—in this country at least—to apply it. The difficulties of applying it are real and formidable, but it is high time that an influential body of hygienists, such as that represented by the present meeting, should get together and decide what ought to be done. Fortunately the speakers who will follow me will be able to report that a start has already been made, and they will be able to inform you of schemes of measles prophylaxis which are in actual operation. In these circumstances I think I can best serve the purposes of the discussion by referring to some of the more general problems, leaving it to others to describe in detail their own work and the successes and difficulties with which they have met.

ÆTIOLOGY OF MEASLES

The first step in the prophylaxis of an infectious disease should be some knowledge of its ætiology, and of the ætiology of measles we know next to nothing. It is invidious, but necessary, to discount the great majority of observations which have been made on this subject. There have been recurrent claims that measles is due to a visible bacterium. The most recent of these have been by Caronia, who has isolated a small Gram-negative coccus; by Tunnicliff, who implicates a green-producing streptococcus; and by Ferry and Fisher, who state they have isolated a similar streptococcus which, they assert, produces a potent toxin. All three claims have been challenged by a majority of workers who have attempted to substantiate them, and I think it is quite fair to state that they have carried no conviction to bacteriologists in general.

In the absence of any clear evidence that measles is a bacterial disease it is customary to consider it as due to an ultra-microscopic virus. For this view there is a considerable amount of support, both direct and indirect. The high infectiousness of measles without any concomitant bacteriological findings, the long "silent" period of incubation, the nature of its exanthem, its rapid evolution and devolution, its great constancy of clinical aspect, and the consistent and lasting immunity conferred by an attack—all these point to a relation with a "virus" rather than with a bacterial disease.

The direct evidence that measles is due to a filterable virus, though perhaps not so solid as the importance of the subject demands, is none the less weighty. In the first place, the only experimental animal which has been shown at all convincingly to be susceptible to the disease is the monkey. Hektoen and Degkwitz have amply confirmed the results of earlier and less controlled experiments, going back to the time of Francis Home, that the

blood of cases of measles in the early stage of this rash is infectious to children. But even here natural infection seems to be much more certain than any artificial method. Regarding the susceptibility of monkeys results have been conflicting, and though Blake and Trask have brought forward very convincing evidence of the susceptibility of *Macacus rhesus* I imagine that few bacteriologists would look upon their demonstration as a closed chapter. Perhaps the most important point in their work is that they appear to have demonstrated that Berkefeld N filtrates of nasopharyngeal washings could produce the disease in monkeys. In monkeys Blake and Trask observed, after an incubation period of six to ten days, conjunctivitis and a macular eruption, accompanied by a leucopenia, and followed by an immunity to further inoculation. It is to be regretted that at the time of Blake and Trask's experiments knowledge of the serum prophylaxis of measles was not enough advanced to suggest to them the counter-check of attempting to prevent their disease in monkeys by previous inoculation with serum. This, had it come off, would have added considerable support to their observations.

POSSIBILITIES OF IMMUNE SERUM

As no domestic animal appears to be susceptible to the disease the only source of immune serum against measles available is the human being who has passed through the disease.

It is to Nicolle and Conseil (1918) that we owe the first experiments suggesting the utility of this serum. Since then many other workers, particularly Debré in France and Degkwitz in Germany, have worked out the details of the method of prophylaxis, the latter initiating the inquiry as to the value of serum taken from adults who have had measles in infancy. As to the value of serum taken in early convalescence, there is a very general agreement among workers throughout the world, many of whom have claimed 80 to 90 per cent. of successes if the serum is properly administered. But it would be unfair to suppress the fact that breakdowns are often met with, due sometimes to factors that are readily explicable but not infrequently occurring when no such explanations are forthcoming.

It is of course very difficult to collect conclusive facts on such a method of prophylaxis as this, and highly infectious as measles is, everyone meets with extraordinary vagaries in its infectiousness. Certainly individual successes in prophylaxis prove nothing. One must remember that remarkable results have been recorded using antibacterial serum and even normal horse serum. It is the cumulative experience derived from many efforts carried out all over the world that persuades us that convalescent serum is a really effective prophylactic reagent.

Practical Aspects

The use of convalescent serum is a procedure of very limited application, and whether the serum prophylaxis of measles is to be established as a practical public health measure will depend very much on the efficiency of serum taken from subjects who have once had measles. This I will call "adult," in contradistinction to "convalescent," serum. The published evidence in favour of its use has not up to now been convincing in all instances, though perhaps to-day we shall hear of valuable additions to this evidence.

Theory as well as experience, so far as it goes, suggests that serum is best collected immediately after the period of defervescence, for at this time such circulating antibody as is present is probably at a maximum. It is not to be supposed that this maximum is maintained

* Read in opening a discussion in the Section of Public Health at the Centenary Meeting of the British Medical Association, London, 1932.

for long. Our available knowledge of the rate of disappearance of circulating antibodies is largely based on studies of diphtheria antitoxin and of precipitin. In both these cases the maximum of circulating antibody is only maintained for a short period, and in the absence of further antigenic stimuli the amount of antibody in the blood soon falls to a small fraction of its original titre. A single antigenic stimulus given to a reactive child may cause the diphtheria antitoxin in the blood to reach 50 units per c.cm. a couple of weeks after the injection. Five weeks later the amount of antitoxin present may be only about a quarter of that amount (Jensen). If the protective antibody in measles follows even approximately the usual formulae of disappearance it is obvious that within a year or two of the attack the antibody remaining in the blood will be negligible, and one would imagine that it would need at least ten times as much adult serum as convalescent serum to serve for prophylactic purposes—namely, 50 to 100 c.cm.; clearly an impracticable dose. It is important, I think, that this theoretical objection be answered by particularly hard facts, if indeed it can be answered at all. There is, however, at least a *prima facie* case that adult serum is of use, and I hope that to-day we will hear more evidence in its support, for the practical applicability of the serum prophylaxis of measles will depend largely on a favourable answer to this question.

PROBLEM OF SUPPLY

The immediate problem is the admittedly difficult one of collecting a sufficient quantity of adult serum for an extensive and scientific trial. Dr. Gunn will tell us how far the London County Council has advanced in this direction, but it is obvious that this body will not be able to satisfy more than its own domestic needs, which are very great. The collection of serum must be made on a much larger scale if we are going to have enough to go round—even for trial. We badly need a central organization to further this work. Young volunteers prepared to part with their blood are perhaps not easy to find, but if more serum has not been collected in this country it cannot lightly be blamed on the public, among whom there are always plenty of generous-spirited individuals, so much as upon the medical profession, which has as yet done very little to organize the service and make the public aware of its necessities.

A Public Serum Service?

With the support of the Medical Research Council and the Ministry of Health, and with the co-operation of the London County Council, we have already started a small-scale volunteer service of serum donors among the students of University College and of University College Hospital Medical School, and we have no reason as yet to think that there is likely to be a failure of a steady flow of volunteers. The difficulty up to now has not been in finding volunteers, but in making use of them.

The removal of 200 to 300 c.cm. of blood from healthy young adults, far from doing any harm, has often been stated by the donor to be a tonic experience. The main practical problem is to remove the blood expeditiously and without pain or inconvenience. Our own experience of blood-letting has convinced us that there is room for improvement in the apparatus generally used for this purpose.

We have devised a simple blood-letting apparatus which we have found useful. The special advantages which we think this apparatus possesses are that it can be used by a single-handed operator and that the serum can be kept sterile and easily removed from the clot.

We always use novocain as a local anaesthetic. If apparatus and operator allow serum to be collected without any hitch I see no reason why volunteers should not be almost unlimited. If a proper appeal were made to the right elements of the public the service might be almost indefinitely enlarged, and, if experience supports the use of "adult" serum, might be put on a permanent basis. One need only mention a few of the organizations to which one would be unlikely to appeal in vain for volunteers—the Red Cross Society, St. John Ambulance Association, Boy Scouts, Y.M.C.A., etc.

I believe that if a scheme were put on foot it would soon justify the appointment of a whole-time medical officer, and until such an officer is provided the work is likely to go slowly, for the harvesting of serum on a large scale is not easy to fit in with other duties. There is also the problem of the further treatment of the serum. The preparation of serum on a large scale for human use is not a responsibility that anyone with experience is likely to underrate, and, under any scheme, would have to be allocated to a serum worker of special competence. Fatal accidents have already been reported abroad owing to the use of contaminated measles serum.

PROPER FIELD OF APPLICATION

If an organized supply of serum were arranged it is obvious that general practitioners and others would have to learn to use it conscientiously, for it would be unlikely that the available supply would suffice for any but urgent cases, such as the protection of sick and weakly children or the prevention of spread in hospital wards and other children's institutions. At least its use should be limited to children under 4 years of age, except in special instances, for not only does the risk to life become almost negligible after that age, but there are many indications that it is much more difficult to protect older children even with the most potent serum.

The family doctor may be faced with the awkward situation that the infant he has successfully protected may be exposed a couple of weeks later to an infection in an older brother or sister whom he has been unable to protect, for it is doubtful if passive immunity with ordinary doses of serum can be expected to last more than a few days. It is generally believed that an attack of measles may be attenuated by doses of serum not sufficiently great to prevent the disease, but that this is in any way a regular and easily controlled effect should, I think, be accepted with reserve pending the collection of more conclusive evidence. Trivial attacks of measles are common enough in uninoculated children, and a decision on the attenuating effects of serum is extremely difficult, particularly as allowance must always be made for the optimistic interpretation of pioneers.

There are two other points which I hope will be dealt with during the discussion: Is there any danger of the child who is apparently completely protected with serum being a source of infection to others? Is there any evidence that sterile human serum ever gives rise to local reactions when injected into children?

I have avoided putting forward any views as to the part public health authorities should play in the furtherance of these prophylactic schemes remembering that Burke says: "It generally argues some degree of natural impotence of mind or some want of knowledge of the world, to hazard plans of government except from a seat of authority." To-day we have a unique gathering of those "in authority" in the public health world, and not the least valuable part of this discussion should be their views on the practicability of a comprehensive scheme for the collection, distribution, and trial of prophylactic measles serum.