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COMBINED ACTIVE AND PASSIVE IMMUNIZATION AGAINST DIPHTHERIA

II. CONTROL OF EPIDEMICS IN THE FIELD*

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In the previous paper (p. 717) evidence was brought to show that by means of combined active and passive immunization a degree of active immunity can be produced which, though slower in its development, is ultimately not greatly inferior to that resulting from active immunization alone.

Attention was drawn to the difficulty in practice of protecting children against diphtheria during the intermediate phase of relative susceptibility which, according to Gundel and König's (1938) experiments on guinea-pigs, probably occurs between the waning of passive immunity due to the injection of antitoxic serum and the development of active immunity due to inoculation with diphtheria prophylactic. Information on the length and degree of this intermediate phase of relative susceptibility cannot be obtained in human beings by the direct experimental method, but the observations of Gierthmühlen and Voges (1939) on children during an actual epidemic of diphtheria suggest that with doses of 0.3 to 0.5 c.cm. of A.P.T. and 1,000 units of antitoxin it is at its maximum between about three and six weeks after the first injection of A.P.T. and serum, and that it is considerably less in degree than the susceptibility of uninoculated children.

Though this information was not available to us when we were conducting the observations about to be described, we were fully aware of the possible occurrence and danger of such an intermediate phase of relative susceptibility. It seemed to us, therefore, that, if an outbreak of diphtheria was to be brought under immediate and complete control, the only satisfactory way to prevent fresh cases from developing during the relatively susceptible phase was by protecting the children so far as possible from further risk of exposure to infection. This we proposed to do by detecting all carriers in the community and segregating them until the remaining children had acquired an adequate degree of active immunity.

Method of Controlling an Outbreak of Diphtheria

The method we adopted when it was evident that an outbreak of diphtheria in a school had begun was as follows:

1. Separate swabs were taken from the nose and throat of all children and teachers in non-residential schools and of the complete staff in residential schools. These were streaked on to a modified Horgan and Marshall tellurite blood agar, and

* Part I, "Studies of Antitoxin Response in Normal Students," appeared last week.

diphtheria bacilli that developed were typed in the usual way. All strains of mitis and of intermedius type were uniformly tested for virulence to guinea-pigs, and a proportion of the strains of gravis type.

2. At the same visit all children were inoculated simultaneously into the left upper arm with 0.1 c.cm. of Burroughs Wellcome's alum-precipitated toxoid (A.P.T.) and into the right upper arm with 350 to 500 units of refined diphtheria antitoxin globulin (Pope, 1938, 1939) contained in about 0.1 c.cm. of serum. All injections were given into the deep subcutaneous tissue. The use of refined serum greatly lowers the incidence of serum rashes (Hutchison, 1939; Parish, personal communication, 1940).

3. All carriers were isolated or segregated as soon as the results of the swabs were known.

4. Four weeks later all children, including the carriers, were given 0.3 c.cm. of A.P.T. into the right upper arm.

5. All carriers were allowed to return to school two weeks after the second inoculation with A.P.T., but, though permitted to mix freely with the other boys and girls, they were forbidden, in residential schools, to participate in games with visiting teams. Any carrier who gave three consecutive negative swabs on tellurite blood agar before the end of the six-weeks period of segregation was allowed to return to school at once.

This general technique was adopted in seven outbreaks of diphtheria for which our help was sought. In the first three outbreaks it was modified by Schick-testing and swabbing the children at the first visit in accordance with the recommendation of Okell, Eagleton, and O'Brien (1924), and giving combined active and passive immunization three days later to the positive reactors. A single dose only of 0.3 c.cm. of A.P.T. was given to the negative reactors to serve as a stimulus to their antibody-producing mechanism. Preliminary Schick-testing was subsequently abandoned owing to the high proportion—75 to 90%—of susceptible children usually met with in the non-residential type of school population with which we later had to deal and to the waste of time involved. Not only did it necessitate an extra visit for the immunizing staff, but it meant the loss of three days in protecting the children at a time when they were most likely to develop infection. Another modification concerned the typing of the diphtheria bacilli, which was not undertaken as a routine in the early outbreaks investigated.

Results

The following is a brief description of our observations on the individual schools:

Royal Merchant Navy School.—This is a boarding school for about 200 boys and 100 girls. Diphtheria broke out, mostly

of the nasal type, in October, 1939. By the beginning of December, 1939, when this laboratory was consulted, some 20 cases had occurred. All the children, as well as the teaching and domestic staff, were swabbed. Schick tests were carried out on the children, but not on the staff. Three days later the Schick tests were read: 58.4% of the children proved positive. With one exception all the Schick-positive children, the children in the hospital and sick bay, the domestic staff, and many of the teaching staff were given 400 units of antitoxin and 0.1 c.cm. of A.P.T. The second dose of 0.3 c.cm. of A.P.T. was given four weeks later. The swabs revealed 21 carriers of virulent diphtheria bacilli; 12 of these were carrying in the throat, 6 in the nose, and 3 in both throat and nose. These carriers were isolated for six weeks—that is, two weeks after the second injection of 0.3 c.cm. of A.P.T. Eight weeks after the second injection the children were re-Schicked. A conversion rate of 97% was recorded. The 3% of children who still reacted positively were given a third dose of 0.3 c.cm. of A.P.T. Two cases of diphtheria occurred after the first visit of the laboratory staff. One was in a boy who was removed from school by his parents without being immunized. The other, which was extremely mild, occurred in March, 1940, in a girl who had entered school in January with a history of having just received one immunizing injection of an undisclosed antigen at home. She was given 0.3 c.cm. of A.P.T. at school six days after her first injection. The interval between the two doses was presumably too short to enable an adequate degree of immunity to develop.

Turner's Court Training Colony.—This is a training colony for males between the ages of 14 and 24, and contains some 300 pupils. At the time of the first visit of the laboratory staff in December, 1939, at least 6 cases of diphtheria had recently occurred, one of which had proved fatal. Owing to the age of the boys, the whole colony was Schick-tested; 36% of the total were Schick-positive. The positive reactors were given 350 units of antitoxin and 0.1 c.cm. of A.P.T., followed four weeks later by 0.3 c.cm. of A.P.T. Nose and throat swabs which were taken at the first visit from all the boys revealed the presence of 11 carriers of virulent diphtheria bacilli. Six of these were carrying in the throat and 5 in the nose. The carriers were isolated for six weeks, but were not treated in any way. The pupils were re-Schicked eight weeks after the second injection. The conversion rate was 97.7%. The two boys who still reacted positively were given a third dose of 0.3 c.cm. of A.P.T. Two cases of diphtheria occurred subsequent to our first visit. One was, a few days after Schick-testing, in a boy whose immunizing record was defective; the other was in March, 1940, in a new boy who had entered the colony in the meantime without being immunized.

Chadlington and Spelsbury.—In these adjacent villages in Oxfordshire 22 cases of diphtheria were reported between January and November, 1939. All except three were in school children. Twenty of the cases had occurred at Chadlington, where the school population was about 120, and two at Spelsbury, where the school population was about 50. Closure of the school at Chadlington on three occasions for a considerable time had failed to prevent the occurrence of further cases. In November, when this laboratory was called in, Schick-testing was carried out on all the available school children, and nose and throat swabs were taken; 76% of the children proved to be Schick-positive. These children, together with those who had not been available for testing, were given 350 units of antitoxin and 0.1 c.cm. of A.P.T. The parents of 13 children refused immunization; these children were therefore excluded from school, together with 3 who were found to be carrying virulent diphtheria bacilli—2 in the throat and 1 in the nose. The school was reopened as soon as the carriers had been isolated. A second dose of 0.3 c.cm. of A.P.T. was given one month later to those children who had received a first dose. No cases of diphtheria occurred in either village after the beginning of immunization. Of the children who had been immunized 87 were re-Schicked ten weeks after the second dose of A.P.T., and a conversion rate of 96.5% was recorded. The two positive reactors were given a third dose of 0.5 c.cm. of A.P.T.

Chippenham.—In a day school containing over 400 children 7 cases of diphtheria occurred within a single week in the middle of October, 1940. The school was visited at once.

Nose and throat swabs were taken from 360 of the children, all of whom were given 500 units of antitoxin and 0.1 c.cm. of A.P.T. No fewer than 27 carriers of virulent intermedius type of diphtheria bacilli were found—22 nasal, 4 throat, and 1 nose and throat. These were excluded from school for six weeks. Four weeks after the first visit the children were given a second immunizing dose of 0.3 c.cm. of A.P.T. Only one case of diphtheria occurred subsequent to our first visit, and that was in a child who had left the school without being immunized.

Lyneham and Tockenham.—In these two small adjacent villages in Wiltshire 9 cases of diphtheria, 2 of which were fatal, occurred between October and December, 1940. The school population numbered about 100. In the beginning of January, 1941, the children were given 500 units of antitoxin and 0.1 c.cm. of A.P.T. At the same visit nose and throat swabs were taken. Six carriers of the virulent gravis type of diphtheria bacilli were found; 3 were nasal, 2 were throat, and 1 was both nose and throat. These children were excluded from school for six weeks. Four weeks after the first immunizing dose the children were given a second dose of 0.3 c.cm. of A.P.T. No further cases of diphtheria occurred.

Leafield.—Two cases of diphtheria occurred in this Oxfordshire village. One was in an evacuee school child in August, 1940; the other was in a local child in November, 1940. Swabs were taken on November 11 and 15 from 170 children and staff, with the result that 22 carriers of diphtheria bacilli were found, all of the virulent mitis type; 4 were nose, 13 throat, and 5 nose and throat. Though cases of clinical diphtheria had been few, it was decided, owing to this high carrier rate, to give combined active and passive immunization to the children. This was done on November 20, when 0.1 c.cm. of A.P.T. and 500 units of antitoxin were injected. Since hospital beds for the isolation of the carriers were not available, these were kept segregated during school hours in a single classroom and forbidden to play with the other children. Two weeks after the second immunizing dose of 0.3 c.cm. of A.P.T., which was given on December 18, they were allowed to return to their normal school routine. No further cases of diphtheria occurred. The failure of this outbreak to assume epidemic proportions in spite of the high carrier rate is of some interest.

West Wycombe.—In August, 1940, 4 cases of diphtheria occurred within a week in the local school. On Monday of the following week the school was visited. Nose and throat swabs were taken from 120 of the children and staff, and the children were given 0.1 c.cm. of A.P.T. and 500 units of antitoxin. Nine carriers of the gravis type of diphtheria bacillus were detected—1 nose, 6 throat, and 2 nose and throat. The carriers were isolated. A second dose of 0.3 c.cm. of A.P.T. was given a month later. No further cases of diphtheria occurred.

Discussion

The results described in these seven outbreaks of diphtheria are very promising. With one possible exception, a boy whose immunization record was incomplete, there was not a single case of diphtheria after the first dose of A.P.T. and serum, whereas at least four cases occurred in children who for one reason or another had not been immunized. It is of course impossible to say what would have happened in the absence of our intervention, but the fact that in two outbreaks several cases had occurred in the previous week, and that in five of the outbreaks a large number of carriers were detected, renders it probable that in some at least of the schools cases would have continued to develop.

The problem created by the intermediate period of relative susceptibility, discussed briefly in the introduction to this paper, appears to have been satisfactorily solved by the detection and segregation of the carriers in the community. Permitting them to return to school a fortnight after the other children had received their second dose of A.P.T., even though they were still carrying the diphtheria bacillus, was admittedly hazardous, but in practice it did not lead to the development of any fresh cases in immu-

nized children. Two cases did occur, however, in children who either had not been immunized at all or had been imperfectly immunized.

It seems clear that if carriers are to be allowed to return to school in six weeks the remainder of the school children should in the meantime have been adequately treated. With the active co-operation of medical officers of health, such as we have been privileged to enjoy, there should be little difficulty in ensuring that all, or practically all, the children are immunized. If for any reason this proved impossible, either the carriers or the non-immunized children would have to be kept out of school, depending on which was the smaller group.

Judging from Fjord-Nielsen's (1940) observations on guinea-pigs, it is possible that a greater and more rapid degree of immunity might be obtained if a second dose of A.P.T. was given two weeks after the first combined injection, and a third dose a fortnight later. This would necessitate an extra visit for the immunizing staff, but it might render safe the liberation of the carriers within four instead of six weeks. No data, however, are available on this point, and it would be wise to make careful observations on the antitoxin production of non-contacts treated by this method before applying it to the control of epidemics in the field. Meanwhile, in view of Glenny, Buttle, and Stevens's (1931) observations, it would probably be sound practice, in order to ensure a greater amount of unneutralized toxoid remaining after the first injection, to increase the first dose of A.P.T. from 0.1 c.cm. to 0.3 c.cm.

It is curious that the method we advocate in this paper—namely, the use of active and passive immunization, and the detection of carriers and their isolation for six weeks—does not seem to have been employed previously, though each has been tried by itself. Ramon (1940), for example, states that the treatment of diphtheria contacts by combined active and passive immunization has been used extensively in France, but he mentions nothing about the detection and isolation of carriers, nor does he give any record of the results obtained. Gierthmühlen and Voges (1939) used the method of combined active and passive immunization in a school epidemic near Hamburg, but as they likewise paid no attention to possible carriers it is not surprising that a number of cases developed after passive immunity had worn off and before active immunity had become sufficiently established. Martin, Loiseau, and Laffaille (1928) used combined active and passive immunization for 14 school contacts, but again they did not attempt to remove the carriers. Okell, Eagleton, and O'Brien (1924), on the other hand, recommend the isolation of carriers but rely exclusively on active immunization of the Schick-positive contacts. The weakness of this method consists in wasting time over the Schick test and in affording no protection to susceptible children who are already infected or who contract infection before the carriers are removed. It would seem that if an outbreak of diphtheria is to be stopped at once, and that if further cases developing from exposure to infection after passive immunity has worn off are to be prevented, both combined active and passive immunization and the detection and isolation of carriers are necessary.

Summary and Conclusions

A method is described for bringing outbreaks of diphtheria in closed or semi-closed communities to an abrupt end.

The method consists essentially in (a) giving combined active and passive immunization to all those exposed to risk, and (b) detecting and segregating carriers of the diph-

theria bacillus. Preliminary Schick-testing is neither necessary nor desirable.

The doses used in our work were 0.1 c.cm. of Burroughs Wellcome's A.P.T. and 350 to 500 units of refined diphtheria antitoxin for the first injection, and 0.3 c.cm. of A.P.T. for the second injection, four weeks later. It might be advisable, however, in future to increase the first dose of A.P.T. to 0.3 c.cm. and to give 500 units of antitoxin as a routine. Refined serum is advisable, because of the low proportion of serum reactions that follow its use. Carriers are immunized in the same way as the other children.

Six weeks after isolation—that is, two weeks after the rest of the school has received its second immunizing dose—the carriers can be liberated and allowed to mix freely with the other children, even though they are still infective. All new-comers must be immunized before entering the school or be kept segregated till they have been immunized.

This method was used in seven residential and non-residential schools in which diphtheria had broken out. The population at risk was about 1,500. In every instance the outbreak ceased immediately. Only five fresh cases are known to have occurred subsequent to the first combined injection: three of these were in children who were not immunized, one was in a child that did not receive its second dose of A.P.T. after four weeks, and one was in a child whose immunization record was defective.

These results are very promising, and it is hoped that other workers will give the method a trial. The fact that the children are protected at once by virtue of the serum injected renders closure of the school quite unnecessary. The saving of time, money, and inconvenience thus effected is too obvious to need stressing.

In outbreaks involving so many different administrative authorities it is impossible to accord due recognition to all the medical officers, head masters, health visitors, and school teachers who helped us. We should, however, like to mention particularly Dr. Campbell, M.O.H., West Oxfordshire Combined Districts; Dr. Rose of Wokingham; Dr. Warburton of Wallingford; Dr. Tangye, County M.O.H., and Dr. Blackley, Assistant County M.O.H., Wiltshire; Colonel Powell, M.O.H., borough of Chippenham; and Dr. Moore, M.O.H., borough of Chepping Wycombe. We are also greatly indebted to Miss D. M. Elliott for her care and help in keeping the records, and to our chief technician, Mr. J. D. Atkinson, whose forethought and continual watchfulness in arranging for the necessary provision of equipment cannot be praised too highly.

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According to the *Klinische Wochenschrift* (May 5, 1941), large quantities of rose-hips, the vitamin C content of which is ten times that of lemons, have been collected in Bulgaria. Roughly seven times the quantity gathered in the same period in Germany was obtained for Germany by a common organization in the two countries. The hips were dried, ground, and packed in Bulgaria, and were sent to Germany to be prepared for consumption. During the months of April and May the hips are to be distributed for sale among selected towns in accordance with instructions issued by the Reich Ministry of Health and the Reich Ministry of Food. Half of them will be given to the troops in Norway and sailors of the fleet, who are in special need of vitamin C, and the hospitals will also receive some.