Original Articles.

FOR WHAT PERIOD OF TIME CAN IMMUNITY FROM DIPHTHERIA BE CONFERRED BY A SINGLE INJECTION OF ANTITOXIN? THE DOSAGE.

BY F. GORDON MORRILL, M.D.,
Visiting Physician to the Children's Hospital, Boston.

WHILE one reads an occasional mention of immunization against diphtheria in the journals, the literature of the subject is vague and unsatisfactory as regards the vital questions, For how long a time can safety be insured, and what is the proper dose of antitoxin? The most satisfactory report which I have seen is that of Dr. Hermann M. Biggs, of New York, "The Use of Antitoxic Serum for the Prevention of Diphtheria," to which I shall have occasion to refer later on. The longest paper, or rather series of papers of which I have any knowledge is that of Kassowitz,¹ who positively denies that the serum confers the slightest degree of immunity. To arrive at anything like a definite and respectable conclusion as to what can or cannot be achieved in the prevention of diphtheria the careful personal observation of a large number of recorded cases during a period of years is required,—and it has been our good (or bad) fortune to have used antitoxin for immunization at the Children's Hospital since January 13, 1895; and while my object in preparing this paper has been to present what I believe to be the truth about immunization, rather than to answer Dr. Kassowitz, I venture to hope that I can at least cast a substantial doubt upon the soundness of his conclusions and the means (in part) by which he has reached them.

An outline sketch of what has been done to prevent the occurrence of diphtheria in our wards, and of the circumstances which led to our adoption of a system which we still employ is as follows:

For years we had been seriously handicapped by occasional outbreaks of diphtheria in the hospital, and during the year 1894 we were obliged to discharge every child in the house and close our doors on three separate occasions. After each of these epidemics we went through a thorough process of cleaning and disinfection, and enforced such rules as to the admission of visitors as seemed likely to prevent a recurrence of the trouble. But notwithstanding these precautions, on January 13, 1895, we were confronted by the serious fact that we had three cases of clinical and six of what we soon learned to regard as bacteriological diphtheria in our infectious ward; and the question of closing the hospital for the fourth time within twelve months, or trying what immunization might do to aid us in keeping our doors open and going on with our work, arose, and the latter course decided upon. Accordingly all the children and nurses were injected, and with complete success so far as promptly stopping the further development of any symptoms which were thought to characterize diphtheria previous to the birth of the Klebs-Löffler bacillus.

At that time there prevailed decidedly vague notions as to what could be accomplished in the way of immunization, and the amount of serum injected for the purpose was too small—150 units being the usual dose employed.

Equally indefinite ideas as to the significance of

the presence of the bacillus *per se* were in vogue, and we fell readily into line with the opinion that this alone constituted diphtheria; and thus fresh terrors were attached to a name which we had already sufficient cause for disliking. So that while we congratulated ourselves upon having escaped a very immediate danger, the question of how often to inject remained to be settled; and while sending all children who had the bacillus but no clinical symptoms of diphtheria to the infectious ward seemed rather a harsh measure, we feared the disapproval of the bacteriologists if we failed to perform what they proclaimed to be an obvious duty, all of which resulted in an overcrowding of the infectious ward, and a great waste of serum, which we used in frequently repeated injections in such cases as had the bacillus, but no clinical symptoms, hoping thereby to rid our patients of microbes which were really doing them no harm.

Each child was injected upon entering the house, and cultures were made to the extent that we were able to impose upon the good nature of the gentlemen at the Bacteriological Laboratory of the Harvard Medical School (who certainly did all in their power to aid us), and deluded with the belief that each new discovery of the bacillus meant a fresh infection, the interval permitted to elapse between the routine immunizations of well children was fixed at thirteen days; so that while the doses given were too small, their frequency made up for this deficiency in a great majority of cases so far as the prevention of clinical diphtheria was concerned. On May 5th the infectious ward was empty, all throats and noses were free of the bacillus, and our experience could be briefly summed up as follows: None of the children who had been sent to the infectious ward with merely bacillary throats or noses had manifested any symptoms of clinical diphtheria, although thoroughly exposed to infection both from their own mucous membranes and from patients having well-marked deposits of diphtheritic membrane.

Two emergency cases had broken down within twenty-four hours of admission and immunization. One boy who had received 150 units January 29th had unmistakable symptoms February 15th; and a girl who had been injected with a like amount broke down March 25th. No antitoxin was used (excepting for curative purposes in cases which I shall shortly mention) after May 15th until the succeeding autumn.

June 30th two girls returned from the Convalescent Home at Wellesley with diphtheria.

July 14th Theresa R., and August 5th William M., were sent over to the infectious ward from the house.

On November 15, 1895, immunization was again begun and our statistics up to that date are: Of 279 immunized children, four had diphtheria—two of these within twenty-four hours after injection and two from the fact (as I shall hope to prove) that the amount of antitoxin used was altogether too small. As to the first two cases, it is merely stating a truism to say that one can immunize too late, just as one may vaccinate too late, and that such cases are merely the natural results of (often unavoidable) delay.

Of 414 non-immunized patients who were in the house between May 15th and November 15th, four had diphtheria; and this at a time when the disease was far less prevalent, and when open windows af-

¹ Vienna Medical Weekly, May 16, 1896.

forded free ventilation for those in the hospital, while the two who broke down at Wellesley had enjoyed plenty of outdoor air.

In view of our previous experience, it was now decided to inject each child in the bath-room on admittance before permitting it to enter any of the wards—the amount to be injected being fixed at one-half the curative dose for children of eight or over, one-third for those between five and eight, and one-fourth for patients between two and five.² No delay was permitted (for bacteriological examination) in the admission of patients, but all new cases were sent into rooms in the last wing, there to remain until their cultures showed their fitness to occupy beds in the common wards. To this section of the house were also sent all cases acquiring the bacillus while in the hospital. The injections were repeated every 28 days, and in case of fresh discoveries of the microbe the children having it were at once injected providing 10 days had elapsed since their last immunization.

December 15, 1895, Dr. H. W. Gross entered upon his duties as bacteriologist to the hospital, and weekly cultures were made from every throat and nose in the house.

During the winter and succeeding spring (1896), although very nearly eight per cent. of the children had the bacillus, and we were free from its presence for five days only, as shown by the cultures, the only cases of diphtheria were: a case in which the antitoxin was accidentally omitted for 36 days, and two who were sent to the City Hospital from Wellesley after omission of immunization for three months and 43 days respectively. By the middle of May all the cultures were negative and injections stopped.

During the summer no cases of diphtheria occurred and we did not resume the antitoxin until November, 1896, when we determined to pay no further attention to the bacillus, but to simply inject every 28 days with the same dose employed during the preceding winter. The result of the previous year being: Of 421 children injected every four weeks, none had diphtheria, while of 425 either non-immunized patients or in whom the serum had been omitted for at least 36 days, three had contracted the disease.

Accordingly, no further cultures were made, and applicants were freely admitted to the common wards. All went well until February 18, 1897, when a boy of ten was sent to the City Hospital from Wellesley 23 days after receiving 250 units. It was not thought best however to shorten the intervals on account of the exception, particularly in view of the fact that an insufficient amount had been used,³ and matters proceeded as before until March 5th, when a girl, age six, who had been given 300 units 23 days previously showed unmistakable symptoms; and again on April 26th, when a child of twelve who had been injected with 400 units 22 days before broke down. May 7th an interne and two nurses and one child (all non-immunized) came down.

Since April 26, 1896, from 250 to 500 units (in accordance with age⁴) have been given each case every three weeks, and we have had no further

trouble. Whether any of the patients have bacillary mucous membranes we do not know; but judging by our previous experience, some of them probably have—just as a certain percentage of children one sees playing about the streets have.

Since November, 1896, of 423 cases immunized every 28 days, three contracted diphtheria, the minimum time elapsing between the infection and clinical symptoms being 22 days; while of non-immunized children and adults four contracted the disease. Of 680 who have been immunized every three weeks none have had it.⁵

Glancing back over what I have said, it will be seen that of 1,808 patients immunized at least once every 28 days with amounts of serum varying from 150 to 500 units, seven had diphtheria; three from insufficient dosing, two within twenty-four hours of being injected, and two in whom the time of infection came 23 and 22 days respectively after being given an amount which has thus far proved entirely effective when given every three weeks. Of 829 who were given no antitoxin, or in whom more than 28 days elapsed after the injections, nine had diphtheria, besides three non-immunized adults.

In New York the results as set forth by Dr. Hermann M. Biggs⁶ are strongly corroborative of the views which our experience has led us to adopt: In the New York Infant Asylum, between September, 1894, and January 16, 1895, there were 107 cases of diphtheria. Two hundred and thirty-four children were immunized on January 17th, and but one case occurred until 30 days had elapsed, when five more developed during the succeeding 12 days at which time an increased dose (125 to 225 units) was given 245 children, and no further trouble was experienced for 31 days. At the Juvenile Asylum 12 cases occurred during the two months preceding April 13, 1895, when 81 children were immunized during that, and the succeeding few weeks,⁷ and the only cases of diphtheria which developed were those of two non-immunized children and one adult. Similar experiences were had at the Nursery and Child's Hospital, the Bellevue and the Catholic Protectory. At the last-named institution the amounts injected at the second immunization corresponded very closely to those which we now employ, and no cases occurred within 30 days, excepting one which appeared within twenty-four hours of the injection. The inspectors of the Health Department immunized 232 persons, and in three of the four cases which broke down within the succeeding 30 days, the symptoms appeared within twenty-four hours—examples of the unavoidable.

Of 1,043 cases tabulated in Dr. Biggs's report (a large percentage having had positive cultures and all having been more or less exposed to infection) three only, aside from those in which symptoms were obscured within twenty-four hours, broke down—on the 12th, 17th and 19th days respectively; and in these three cases the dose administered varied "from 100 to 250 units"—examples of insufficient dosage—while at the Catholic Protectory (where only one break-down and that within twenty-four hours occurred) much larger quantities were used. Surely these results are enough to prove that there "is something in" immunization—something which not only

¹ From November 15, 1895, to March 16, 1896, the serum made by Dr. Ernst was used; and the test of potency being based on the French system, affords no satisfactory means of comparison with the present standard in units. Since the last-mentioned date we have been supplied by the State Board of Health, and the dosage fixed by the prevailing standard.

² Probably on account of a temporary deficiency of serum.

³ The patients at the Boston Children's Hospital are from two to twelve years of age, inclusive.

⁵ Immunization has been carried out during the past summer.

⁶ Loc. cit.

⁷ Interval between injections not stated.

saves life, but does so with a degree of certainty which vaccination alone can rival.

Dr. Kassowitz bases his theory of the utter futility of immunization partly upon the fact that the disease itself confers no immunity from early or late reinfection even in cases treated with the serum, and partly on cases which he quotes when antitoxin has failed to ensure safety. As to reinfection after diphtheria, I am perfectly willing to concede that there is scarcely a disease which a human being cannot have a second time if he survives the first attack; and as to his instances of quite speedy relapse after the serum treatment it might be asked if they may not have been due to failure to use a sufficient quantity during the original seizure.

The cases which he cites as proving that antitoxin administered to healthy children confers no immunity are for the greater part quoted without reference to the journals in which they were originally published, and without stating the number of days elapsing before infection took place—thus rendering fair criticism impossible. Of the few he mentions with definite references, some have proved inaccessible to me, but in any event his cases include: twelve brothers and sisters who accompanied diphtheritic children to the hospital, and who were each injected with 120 units. Three of those who were given this insufficient dose had diphtheria at some indefinite time later on. Two cases in which infection took place in twenty-four hours, and which merely substantiate the fact that one can immunize too late. One case in which an inadequate dose (150 units) was followed by infection on the 18th day. One case in which there was infection on the 28th day.

I do not wish to be understood as implying that the cases which I have not read in their original sources of publication may not carry a degree of belief in Dr. Kassowitz' theory. To do this would be to question the good faith which doubtless inspired him to publish his articles. I can only say that from the material at my command, and an experience of nearly three years in this special line, I can arrive at nothing but a total disagreement with his expressed opinion.

So far as bad results from the injections are concerned, the only cases which I have seen where anything like dangerous symptoms appeared were those of a boy with a splenic leucocythemia, and another with a nephritis. In the latter instance the antitoxin caused a distinct increase of the albuminuria and dropsy. In another case in which the same clinical symptoms were present and the urinary analysis corresponded very closely to that of the first, the injections produced no unpleasant effects. We have given in all about 3,000 injections; and with the above exceptions, aside from an occasional urticaria (far more rare now than formerly) and an insignificant and transitory albuminuria, nothing worth noting has followed them. Very rarely has the antitoxin been omitted or postponed, no matter how sick the patient may have been. In one instance of very severe cerebro-spinal meningitis in which no injections were given, the child contracted a diphtheria which proved fatal.

I am quite sure that the fact of our ability to confer safety for a definite time by promptly injecting exposed cases with an adequate dose of antitoxic serum is not sufficiently recognized; and I think that the prevailing opinion among the medical profession re-

garding immunization may be briefly stated as follows: It is an uncertain thing at best, and perhaps it is, upon the whole, just as well to watch exposed cases, and inject promptly the first moment that symptoms of diphtheria appear. Should advice of this kind be given as regards vaccinating persons exposed to small-pox it would be just as logical—yet these principles are printed, preached and practised to-day, and the point that it is an obvious duty to immunize every person who has been exposed to diphtheria is either denied, or dodged by half-hearted approval, and the recommendation of insufficient doses.

From actual experience we are perfectly justified in believing:

(1) That immunity in any given case, of no matter how thorough exposure to diphtheria, may be conferred, for at least ten days, by the injection of a small dose (100–250 units) of serum, provided it is given twenty-four hours previous to actual infection.

(2) That a larger dose (250 units for a child of two, up to 500 units for one of eight or over*) will confer safety for three weeks—or to be a little more conservative, let us say twenty days—under similar conditions.

(3) That no harm will result from the treatment in a vast majority of cases of sick children, and probably in no case of a healthy child, provided the serum used is up to the present standard of purity.

In conclusion, I would say that any one who thinks that antitoxin will prevent the occurrence of a follicular tonsillitis or of a coryza in an individual who happens to have the Klebs-Löffler bacillus in his throat or nose will be disappointed; for neither of these conditions constitutes a diphtheria any more than the coexistence of the pneumococcus in the saliva and a bronchitis constitutes a frank pneumonia. I will add that a physician who fails to promptly immunize the members of a family or close community in which diphtheria breaks out, neglects to do his duty by those whose safety lies in his hands.

PYONEPHROSIS.

A CLINICAL STUDY, WITH DETAILED REPORT OF A CASE OF EXTREME TYPE.

BY ALBERT H. TUTTLE, M.D., CAMBRIDGE;

EDWARD REYNOLDS, M.D., BOSTON;

AND J. BERGEN OGDEN, M.D.,

Assistant in Chemistry, Harvard Medical School; Assistant in Clinical Pathology, Boston City Hospital.

(Concluded from No. 8, p. 177.)

REMARKS OF DR. REYNOLDS.

THIS case furnishes a fine example, both of the value and the limitations of the ureteral catheter in the treatment of pyonephrosis.

In my opinion this patient would certainly have died if subjected to the knife when I first saw her, and I think that the very remarkable improvement which followed the drainage of the abscess through the catheter must be considered to have saved her life by permitting her to improve to a point at which

* It can readily be conceived that in the employment of large quantities of serum the doses given (for economical reasons, or as a matter of convenience) not always correspond to those which our experience at the Children's Hospital has shown to be the most advisable. For instance, if a phial contains 1,600 units and four children between the ages of eight and twelve require immunization, 400 units would probably be given in each case, and so on.