Experiences with Diphtheria Toxoid in Canada*

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VACCINATION against diphtheria in Canada, as elsewhere, is of recent origin. The employment of Ramon's anatoxin or diphtheria toxoid, as it is more widely known in the United States and Canada, dates back to 1925. Prior to that time diphtheria toxin-antitoxin mixtures had been used in a few communities in Canada, chiefly in the provinces of Ontario and Saskatchewan, on a moderate scale. Beginning in the autumn of 1924 laboratory investigations confirmed the observations of Ramon that this material was, if prepared according to the directions of Ramon himself, (a) quite innocuous, if employed in proper doses, (b) highly antigenic, and very stable (*60° C. for 3 hours*), (c) quite readily prepared, if supplies of potent diphtheria toxin were available for the purpose, and (d) susceptible of reasonably satisfactory assay by means of protection tests using lethal doses of diphtheria toxin, in guinea pigs; skin tests in rabbits or guinea pigs; or by means of the flocculation test of Ramon.

This incomplete list of the advantages which toxoid possesses may be supplemented by the statement that results obtained in the vaccination of a group of young adults revealed the fact that the immunizing qualities of this prophylactic were as readily demonstrable in human beings as in experimental animals.

Upon the completion of this preliminary work, arrangements were made in a number of centers for more extended use of diphtheria toxoid prepared in the Connaught Laboratories. These further trials, notably in Hamilton, Windsor, and Brantford, Ontario, were eminently successful. Very quickly the use of toxoid spread to other parts of Canada and soon its employment upon a large scale was undertaken. This very satisfactory state of affairs has continued, and in the past 6 years sufficient toxoid for the vaccination of over 1,000,000 persons has been distributed in the Dominion.

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Since the methods of preparation and testing are well known and have previously been presented in meetings of this Association, they will not be dealt with at this time. However, certain additions to knowledge of the subject which it is believed have accrued from studies carried on in this country seem worthy of brief reference. In this category may be included the observations which have revealed the fact that it is possible to adjust the dose of toxoid so that local and general reactions of any degree of severity can practically be avoided. From the outset, insistence upon the importance of early vaccination against diphtheria has been frequently reiterated. The time of election is the preschool age period and any time after the 1st year of life seems to be suitable. Again, a thoroughly critical appraisal of the results of large scale employment of toxoid has recently been made in Canada. The results of these studies of McKinnon, Ross and Defries have recently been published. Quantitative estimation of the antigenic response to injections of toxoid has been carefully recorded by Drs. Donald T. Fraser and P. J. Moloney and Miss C. J. Fraser. It is desirable, perhaps, to deal at a little greater length with some of the points above referred to.

In the period 1921–1924 in Canada, diphtheria ranked first as a cause of death of the age group 2–14 years. It accounted for over 15 per cent, or 1 in every 7 of the deaths in that age group. The annual mortality rate per 100,000 population varied from 14 to 23. The number of deaths in a year varied from 1,281 to 2,072. In general, throughout Canada the mortality rate has been falling during the past 30 years while the morbidity rate has remained practically stationary. It is highly significant that approximately one-quarter of the cases and one-half of the deaths occur in the age group under 5 years.

When toxoid was first distributed in Canada, 2 doses were recommended. Blood titration for antitoxin content, however, showed that 2 doses produced 1/25 unit or more of antitoxin per c.c. of serum in 70 per cent of the vaccinated persons. This finding led to the addition of a third dose which, as will be shown, increased the percentage to a satisfactory level. Blood titration in various groups has shown that 3 doses result in the production of 1/25 unit of antitoxin in fully 90 per cent.

As mentioned previously, the recognition and detection of persons who might react unfavorably to toxoid was rendered possible by the introduction of the reaction test by Moloney. Further work has shown that such individuals are readily immunized without accompanying reactions if given graduated doses of toxoid.

The material used in the reaction test is suitably diluted toxoid.

One-tenth c.c. is injected into the skin of the forearm. The size and degree of the reaction in 24 to 48 hours is an index of the reaction which may be expected if prophylactic doses of toxoid are given. The test is used as a gauge of the individual's sensitivity to toxoid. For convenience the readings of these tests are recorded as 1 +, 2 +, or 3 +; 1 + signifies an area of redness no greater than 1 cm.; 2 + an area of redness greater than 1 cm., but with little or no induration; 3 + indicates definite induration at the site of the injection. Canadian experience, notably that of Burke and his colleagues, has shown that individuals who exhibit a negative, or a 1 + reading, can be given the regular dosage of toxoid without question. Those showing a 2 + reading should be given smaller doses, and the few showing a 3 + should be given a specially diluted toxoid. To facilitate the immunization of such markedly sensitive individuals, suitably diluted toxoid is now distributed in Canada. In over 30,000 children in Toronto, in whom the reaction test readings were recorded, the vast majority, 84 per cent, had no reaction or at most a very slight one. These school children were given the regular dosage without showing subsequent reaction. Five per cent of this large group showed a 2 + reading. These were given smaller doses without producing significant reactions. The readings in these 30,000 children show too that the degree of reaction to the reaction test, and therefore to toxoid, varies with age. In preschool age children, a very small percentage showed any reaction to the test and none showed redness of any significant degree. As the child grows older and perhaps becomes sensitized by contact in a diphtherial environment, he is more likely to show reaction. Of those in the school age group of 5–14 years, 10 per cent exhibited a 3 + reading, this being confined chiefly to the older children. Our experience has also shown that those who do present reaction to the test are more readily immunized than others, so that very small doses of diluted material serve in the vast majority to bring the antitoxin content up to the requisite level.

The results of toxoid immunization can be measured in three ways:

1. By testing (Schick tests or blood titration)
2. By comparing the amount of diphtheria in a group of adequate size who have received toxoid, with the amount of diphtheria in a group of the same age distribution and living under similar conditions but not given toxoid
3. By comparing the morbidity and mortality rates in a community before and after the use of toxoid

Blood titrations before and after immunization have shown that in individuals who had less than 1/50 unit before immunization, 90 per cent had 1/25 unit or more antitoxin after receiving 3 doses of toxoid.

In the analyses of the diphtheria cases which occurred in 16,829 Toronto school children who were given 3 doses of toxoid, 0.5 c.c., 0.5 c.c. and 1 c.c. at intervals of 3 weeks, and 8,994 who were given 2 doses of toxoid, 0.5 c.c. each with a 3-weeks interval, and observed for a period from 1 to 3½ years, it has been estimated that during the period of observation, had diphtheria occurred in the treated children at the same rate as in the control group of the same age and under the same conditions of exposure, namely, that of the public school, there would have been expected 222 cases in those given 3 doses of toxoid. There were actually 23 cases reported and among these not one death occurred. This is a reduction of 90 per cent for the whole period. In the first year following immunization the reduction in diphtheria was from 95 to 100 per cent. In the 8,994 children given 2 doses, 200 cases might have been expected; 52 were reported, a reduction over the whole period of 74 per cent. An interesting parallelism between the antigenic response in individuals vaccinated with toxoid and the degree of community protection against diphtheria which resulted is evident in the above figures. The results of the assays of the serums of those given 2 doses of toxoid showed that about 70 per cent were immune and the statistical evidence indicates a reduction in diphtheria mortality in that group of 74 per cent. Furthermore the percentage of individuals immunized when 3 doses of toxoid were given, as determined by blood titrations, was 90 per cent and the reduction in diphtheria mortality in the group of Toronto school children was 90 per cent.

The results in Hamilton, with a population of 150,000, and Brantford, with a population of 18,000, may be quoted as examples of municipalities that have practically eliminated diphtheria. Other experiences such as that in Windsor might also be quoted. Data from the province of Manitoba recently presented by Dr. F. W. Jackson suggest that widespread immunization in that province is a factor which accounts for the unprecedentedly low figures of diphtheria in the past year and the first months of this year.

The efficiency and practicability of toxoid, properly prepared, as an immunizing agent against diphtheria, is established.