IMMUNIZATION IN THE PREVENTION OF SPECIFIC FEVERS*

BY

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From a recent paper I note with some, perhaps forgivable, tendency to a breach of the tenth commandment that when Dr. W. H. Park in New York wishes to compare the relative values of different methods of immunization—for example, by toxoid, given in different doses at different intervals, and with or without the addition of alum—he first investigates the problem, as we do, with laboratory animals, and then repeats the same investigation simultaneously on large groups of comparable children in schools—an opportunity which we in England can regard but with envy. Our English evidence has more of the “before taking” and “after taking” flavour.

Immunization in Diphtheria

Dudley recently recorded that before active immunization there were at the Greenwich School about forty-three cases of “diphtheria” each year, while in a comparable population, after immunization was adopted, the notified cases of diphtheria averaged eight each year for five years; of these cases only eight were clinically recognizable as diphtheria, and in six of them the boys were not yet inoculated. Our own endeavours enabled us to say that from 1921 to 1932 we had kept almost entirely free from diphtheria a school of about 600 children in which twenty cases had recently occurred. Similarly, it has been possible to keep the nursing staff of a large hospital almost entirely free from diphtheria for some five years, without causing any interruption of duty owing to reactions. Two years ago Dr. Parish showed that with toxoid he could produce within about six weeks a state of complete Schick-negativity in 95 per cent. of children in a home, and an appreciable immunity in another 5 per cent.: thanks to the Moloney-Fraser intradermal toxoid test immunization could be carried out without interference with school work. Those who wish to consider what has been done in England will find the details abundantly recorded in Dr. Forbes's book.

If we look at the recent past we find that reasonably good immunity was obtained by the “mixtures” toxin-antitoxin or toxoid-antitoxin, and the first sound evidence that immunization on the large scale was practicable was provided by these prophylactics. At present the “mixtures” are gradually losing favour, except toxoid-antitoxin floccules (T.A.F.), which apparently contains “pure” toxoid precipitated with serum globulin and is free of other “non-specific” substances. At all events, it very rarely causes “reaction,” and is the antigen of choice for people who show a positive Moloney-Fraser reaction.

TOXOID AND ALUM-TOXOID

Toxoid alone is being more freely employed all over the world, and on the large scale in Canada. In Europe and the U.S.A. it has been found to make well over 90 per cent. of Schick-positive reactors negative when given in three, or even two, well-spaced doses. Toxoid is apt to cause troublesome local reaction, except in very young children, but this tendency is being circumvented in several ways. Some workers administer a full dose of 1 c.cm. to all children under 5, and at this age troublesome reaction is rare. For older children the Moloney-

Fraser intradermic test may be applied: the full dose of toxoid is injected into the Moloney-negative reactors and T.A.F. into the Moloney-positive. A good plan is to give what we have called the “universal” dose to all children—for example, 0.1 c.cm. or 0.05 c.cm. Dr. Chesney of Poole injects all children with a small “detector” dose to identify those likely to suffer reaction after inoculation. Toxoid combined with an immobilizing agent—for example, alum—is also being much used. Innocuous tapioca has been demonstrated by Ramon to have the same property—that is, of causing a retention of the toxoid locally over a long period. Glenny and Buttle showed that the tissue at the site of inoculation when excised some days later and injected into another animal immunized this second animal, and recent American evidence indicates that toxoid may be present in the local “lump” for a much longer period, during the whole of which it is being slowly absorbed and is producing immunity.

What of the future? Alum-toxoid—a discovery made by Glenny, Pope, Waddington, and Wallace—has recently attracted the deep interest of the medical public: the antigen has proved of remarkable service in animal immunization in the laboratory, but I am not yet wholly convinced that it will, for human immunization, displace formol-toxoid, which in two well-spaced doses immunizes rapidly. Apparently in certain “sensitive” children there is a liability to reaction due to the remaining non-specific materials present in the toxoid, as well as the tissue reaction or induration caused by the foreign body, alum, or a complex, alum-toxoid. In the U.S.A. special regulations have been framed for ensuring the potency and other requirements of alum-toxoid, but it is understood that the possibility of a reaction is giving the responsible authorities some concern. C. G. Pope has tested intradermally and subcutaneously in guinea-pigs a number of precipitated toxoids kindly supplied by American colleagues and in wide clinical use. While the tendency of different preparations to cause local reaction in the animal varies considerably, the evidence does not suggest that the American preparations provide better results in this test than some of our own, which seem to be attended by an undesirably high incidence of reaction in the limited number of human observations hitherto open to us. These persistent “lumps” and rare “sterile abscesses” still disturb the picture. C. G. Pope has recently carried out a long examination of the phenomena which happen when various percentages of alum are added to toxoid under different conditions, and has prepared precipitates with a minimal content of alum but a very high toxoid content. The work is promising, and is being pursued.

If we had clinical opportunities we should much like to test whether we can immobilize toxoid for a sufficient period in the tissue with substances less irritant and more absorbable than alum, which would slowly release the toxoid and maintain antigenic stimulation for a sufficient period.

SPECIFIC AND NON-SPECIFIC SUBSTANCES

What are our further aims? When the diphtheria bacillus grows in broth there are finally present at least three substances, or groups of substances, which must be dealt with before the ideal immunizing prophylactic can be prepared:

1. The first is specific toxin. This, as we know, can be turned into harmless but antigenic toxoid by various agencies, the most convenient of which is formalin, producing the well-known toxoid called “formol-toxoid,” or, on the Continent, “anatoxine.”

2. Secondly, there are a large number of “non-specific” substances—for example, various proteins, amino-acids, salts,

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etc.—in the original broth, and also others of the kind produced by the metabolism of the growing diphtheria bacillus. Many attempts have been made to get rid of these substances. By precipitation, by dialysis, etc., most of the nitrogen can be removed. My colleagues, Mr. Pope and Miss Llewellyn Smith, made toxoid containing only 2 per cent. of the original nitrogen per Lf unit. By modification of the alum method of precipitation, elimination of nitrogen-containing bodies can be carried still further.

3. Thirdly, it almost appears as if the diphtheria bacillus, when building up molecules of specific toxin, gives rise to, as part of the same molecule, another substance undestroyed by heating, which in certain individuals causes the well-known "pseudo-reaction." If this supposition is correct we shall not entirely abolish the liability of unusually "sensitive" people to local and general reactions after the injection of any diphtheria prophylactic unless we can deprive the diphtheria toxin molecule of this "pseudo" constituent, for apparently the same substance, or complex, causes the "pseudo" reaction, the positive reaction in the Moloney-Fraser test, or the local reaction in the "anatoxi-reaction" described by Ramon, and the troublesome local and general reaction which may follow the injection of prophylactic. This supposition is reasonable, for the percentages of people showing these three phenomena are related.

When the chemist can make pure crystalline toxin as he now makes ferments and vitamins we can expect more rapid progress. The biochemist is making always "purer" toxin and toxoid. Jensen has prepared concentrated toxoid of high Lf value. C. G. Pope kindly allows me to say that by absorption methods he has recently prepared a toxin with a very much smaller nitrogen content per L+ or Lf than he has ever previously succeeded in doing. Further progress along these lines is eagerly awaited. I believe that until we can eliminate the "pseudo" constituent we shall not bid glad farewell to the local swelling and general malaise which may follow inoculation in certain people. Before leaving this aspect of the subject I may be pardoned for again calling attention to the efficiency of the method of dealing with an institutional epidemic which was described in 1923 (*Brit. Journ. Exper. Path.*, 1923, iv, 29)—that is, Schick-test and swab everyone; immunize immediately the Schick-positive children; and isolate and examine daily the Schick-positive and swab-positive children, for it is in this group that you will catch all the cases of diphtheria. (Within the past twelve months we have a record that diphtheria attacked more than one-quarter of the nursing staff of one moderately large hospital.)

TYPES OF DIPHTHERIA BACILLUS

The interesting investigation of the "gravis" and "intermediate" types by McLeod and his school suggests the question, Will our current methods of immunization secure immunity against all types of diphtheria? Robertson and Marshall in their Manchester work recorded eight cases of the throat affection long ago described by Harries as "tonsillitis in Schick-negative carriers"; they also recorded one "severe" and three "moderately severe" infections with gravis bacilli in people recorded as Schick-negative (the full immunological data were not reported). Dudley's exhaustive work at Greenwich suggests that the Schick-negative condition produced by immunization with the ordinary prophylactics gives a slightly lower degree of immunity against gravis infections than against mitis, but his conclusion is that, even in infection of the throat of a Schick-negative child, the clinical result is usually trivial. Further, Parish injected a considerable number of gravis cultures, in fatal doses, into more than fifty guinea-pigs which had been rendered Schick-negative by the ordinary prophylactics of various kinds, and found that the animals

were immune. In "field trials" on huge numbers of human beings in America, Canada, and on the Continent, prophylactic made from the classical Park-Williams 8 strain seems to have given adequate protection. We are justified, therefore, in the absence of other evidence, in directing all our efforts at the moment towards an improvement of the type of prophylactic hitherto made from the Park 8 strain.

IMMUNIZATION AND THE CARRIER RATE

Has inoculation any remote effect on the uninoculated? Dudley has recently recorded that, following immunization of part of a group of boys in the Greenwich School, the "virulent carrier rate" rose, and therefore the risk of attacks of clinical diphtheria increased for those not yet inoculated. Dudley, with his characteristic caution, warns against assuming that this phenomenon would happen generally. I was naturally deeply interested in this suggestion. I believe I am right in saying that a similar argument was at one stage urged in opposition to the proposal to introduce antityphoid inoculation in India and elsewhere, and that experience provided no justification for the argument.

We had ourselves, in several instances, watched a small group of people during immunization, and had seen no indication of increased danger to those not yet immunized. I wrote to a number of leading authorities in the U.S.A. asking what their experience had been, and received permission from E. S. Godfrey and W. W. Lee and others to say that they were impressed with the fall which follows immunization, and that, so far as their experience and consideration of American figures formed a guide, they found no evidence that the morbidity or mortality rises even temporarily in a partly immunized community because of the suggested rise in carrier rate among the inoculated. I know that some other leading authorities in the U.S.A. hold the same view. I may here refer briefly to a recent review by Das. It has always been something of a mystery that clinical diphtheria is so rare in tropical countries. The Schick-negative rate is high and the virulent carrier rate seems to be substantial, yet diphtheria rarely occurs among either natives or introduced Europeans. There is no indication that by any laboratory test the bacilli existent in these regions differ in any way from those causing severe and fatal diphtheria in temperate countries. These still remain something to explain.

Scarlet Fever Immunization

In connexion with immunization against scarlet fever, there is, unfortunately, little new to report. Active immunization with a small series of doses of toxin gives high protection against scarlet fever. J. G. FitzGerald (*Canadian Pub. Health Journ.*, 1933, xxiv, 455) found that, since all Dick-positive nurses at the Children's Hospital, Toronto, have been regularly immunized, the incidence of scarlet fever has been from 0.4 to 0.7 per cent., whereas previously it was from 5 to 6 per cent. It will be remembered that Harries and Benson in this country supplied similar satisfying evidence a few years ago.

Several workers have aimed at shortening the tedious course of four or five injections. In 1929 Ramon and Debré (*Compt. Rend. Soc. Biol.*, p. 1035) formalized toxin and injected children. The immunity obtained was moderately good, though the course could not be reduced to less than three injections, and reactions occurred in about half the children. From the absence of recent publications, it may be concluded that the method has not yet established itself. Ando and Ozaki, in the Dairen work, perhaps provide the clue. As the intensity of

formalinization is increased, the toxicity is reduced, but, unfortunately, so also is the immunizing efficiency. Veldee has studied the method extensively during the past few years. He inclines to the view that formalinization must not be carried too far; unless approximately 500 skin test doses of toxin per cubic centimetre are left, high immunity is not secured, even with three doses and with the addition of alum. Here again it must be pointed out that experience indicates that progress would be more rapid in England if opportunities for immunizing large comparable groups of children were available. R. A. Q. O'Meara and H. J. Parish kindly allow me to say that they have been working with toxin-antitoxin mixture and with floccules as immunizing agents, but the few results available do not yet warrant publication. G. A. H. Buttle has been endeavouring to immunize rabbits rapidly by several modifications of the ordinary methods and by the use of the toxin of unusually high value described by O'Meara, but has not yet obtained results that satisfy him.

Whooping-cough

The work of Madsen in Scandinavia and Sauer in U.S.A. offers considerable hope. Madsen states that of 1,800 people vaccinated 25 per cent. escaped infection, whereas only 2 per cent. of 450 non-vaccinated people escaped. Sauer found that of 380 young children who were vaccinated and suffered exposure not one became infected. An odd feature is that, while Madsen finds that children rapidly become immune, Sauer does not expect adequate immunity to develop for about four months. Jundell in Sweden vaccinates adult volunteers who have had an attack in the past, and hopes in this way to raise the titre of the antibody in the blood, thus obtaining an equivalent of the invaluable "convalescent measles serum" for protection of groups of young children in contact with sufferers from the disease.

General Note

Two thoughts may occur to the practitioner who is interested in this field of work. Reflecting on the resistance of the average parent to vaccination in any form, he will perhaps conclude that if the enthusiast gets his way there will be too much immunization. He must then remember that diphtheria alone causes 40,000 to 60,000 cases a year in England and 2,000 to 3,000 deaths, and that if we adopt Dr. Glover's estimate of the loss of time due to infectious disease in large schools the lost educational time must cost the community a huge sum each year.

The second thought will probably be one of some regret that progress is so slow. The lag is almost wholly on the human side. The immunologist, in England at all events, is always far ahead of the clinical investigator; with greater opportunity of using, under proper safeguards, different antigens on large groups of children, we should progress faster.

G. Serdaris (*Thèse de Paris*, 1934, No. 64) describes the antimalarial campaign carried out in a period of six months in a small area (Rhododaphnia), of the Peloponnese under the auspices of the International Health Division of the Rockefeller Foundation and the School of Hygiene of the Athens Ministry of Health. Although a definite opinion cannot be expressed until the end of three years, the results hitherto obtained have been very good. The number of *A. maculipennis* and *A. superpictus* has considerably diminished, and the splenic index has decreased, while the haematological index has increased. Quinine salts only were used for treatment.

IRRADIATION TREATMENT OF MALIGNANT INTRATHORACIC TUMOURS

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In September, 1927, one of us (F. G. C.), with Dr. Carlyle Potter, published a follow-up of cases of malignant intrathoracic tumour treated by x rays.¹ The results were most discouraging, for out of fifty-nine cases one alone survived. The result in this case, however, was so remarkable that it was impossible to do otherwise than encourage further trial and further development of the treatment. The patient, a young woman aged 25, was under the care of Lord Horder in St. Bartholomew's Hospital in 1923. She was desperately ill with a large mass in the mediastinum, many large glands in the neck, and bilateral pleural effusion. Microscopical examination of a cervical gland showed lymphosarcoma. She still survives in excellent health, and the skiagram is absolutely normal.

The authors of the article were unable to report any prolongation of life, apart from this one instance, and only temporary or no appreciable alleviation of symptoms. In the last few years, however, the results from treatment have seemed to the present authors to be better. Many impressive cases of relief of symptoms have been noted, and also the complete disappearance of the mass in the chest in several instances. It seemed desirable, therefore, to make another investigation into the results of treatment in a series of more recent cases.

Diagnostic Criteria

The first criterion is the proof positive—namely, microscopical examination of a section of the thoracic growth or of a metastasis. This must be accepted as the most convincing evidence, in spite of occasional difficulties of interpretation. The material for examination has been obtained by thoracotomy in seven cases, by bronchoscopy in seven cases (this excludes cases subsequently confirmed by post-mortem examination, otherwise the number would be larger), by removal of a metastasis in five cases, and from post-mortem material in nineteen cases.

The second criterion is clinical evidence: symptoms, signs, course of the disease, and exclusion of other conditions by special investigations. The third is radiological evidence.

It would occupy much space if we attempted to elaborate the last two criteria, nor is it perhaps quite within the scope of this paper. We can say, however, that no doubtful case has been included, and we are confident that the rigid criteria adopted would be accepted by all workers as adequate proof. The few difficult or doubtful cases are described in some detail later.

Our material consists of seventy cases from St. Bartholomew's Hospital, the Royal Chest Hospital, Victoria Park Chest Hospital, and private practice, from 1927 to 1933.