PREVENTION AND TREATMENT OF DIPHTHERIA.*

BY

J. D. ROLLESTON, M.D., M.R.C.P.,

Medical Superintendent, Western Fever Hospital, London.

THE unflagging interest taken in the subject of the prevention and treatment of diphtheria, which appeals alike to the general physician, pediatrician, hygienist, and bacteriologist, is shown by the fact that this is the fifth time within two and a half years that I have been honoured with an invitation to open a discussion more or less directly connected with the subject. A certain amount of repetition of what I have said on previous occasions is therefore inevitable, but I have endeavoured to bring my remarks up to date.

The question of prevention may be considered under two headings—namely, (1) general measures, including isolation, disinfection, and treatment of the carrier; and (2) specific immunization.

GENERAL MEASURES.

Although it is doubtful whether isolation of diphtheria patients in special hospitals has had much effect in reducing its incidence, there is general agreement among sanitary authorities that diphtheria is a disease which, more than any other of those admitted to fever hospitals, requires such treatment. Not only does the laryngeal type of the disease need close and skilful supervision, but the prevention, detection, and treatment of the various forms of post-diphtheritic paralysis are best carried out by a resident medical and nursing staff.

As regards disinfection, there is a growing tendency, which is carried out in practice by several medical officers of health, superintendents of fever hospitals, and other sanitary authorities, to discredit the value of terminal disinfection after diphtheria, and to regard the living carrier, whether actually suffering from diphtheria or not, as responsible for the spread of the disease.

The period of isolation of a diphtheria patient should be determined by clinical considerations. In the absence of any discharges from the nose or ear, or acute inflammatory condition of the throat, a patient who has had a mild attack may be set at liberty at the end of a month. In cases of any degree of severity the period of detention should be prolonged to at least six weeks, most of which should be spent in bed, as during this time some form of paralysis is likely to develop. In the great majority of cases the throat becomes free of diphtheria bacilli within a few days after the membrane has disappeared, and only a small minority persist as carriers of virulent bacilli.

No uniformly successful method has been discovered for putting an end to the carrier state. Various lotions, gargles, and pastilles have been tried, with a varying degree of success, but the results are not convincing. The persistence of the carrier state is usually due to some local infection, such as chronically inflamed tonsils and adenoids or affection of the nasal sinuses. This is strikingly proved by the most efficacious if not the only remedy for the carrier state apart from the *vis medicatrix naturae*, being tonsillectomy and treatment of sinus infections. Tonsillectomy, however, and other surgical measures are not always practicable, nor, indeed, universally successful. In the absence of any morbid condition of the throat and nose the practice of insisting on one or two negative faucial and nasal cultures before discharging a patient is merely illusory, as owing to the frequent occurrence of intermittency in the carrier state a false sense of security may be afforded by such cultures. In their recent investigation J. E. McCartney and W. Harvey did not consider a carrier as free from bacilli until six consecutive examinations, spread over a period of six weeks, produced negative results.

As it has been found that the return case rate in those hospitals which have abandoned the practice of swabbing patients before discharge is no higher than in those in which it is still observed, since my appointment as medical

superintendent two and a half years ago I have discontinued the practice at my own hospital without finding that this discontinuance was followed by an increase in the return case rate.

SPECIFIC IMMUNIZATION.

No invariably effective method being available for putting an end to the carrier state the most reliable method of prophylaxis of diphtheria consists in specific immunization.

Passive immunization by injection of antitoxin has never been used to a very large extent in this country compared with the Continent and the United States for protecting the other members of a family or community in which a case of diphtheria has occurred. The immunity which injection of antitoxin confers, though immediate, is only of short duration, being rarely longer than three or four weeks. The method also renders the patient hypersensitive—that is, liable to have an unusually severe reaction when a therapeutic dose is administered in the course of the next few years. It is further said to interfere with the subsequent process of active immunization, because the injected mixture has been rendered too much over-neutralized to ensure a response. The substitution of cattle serum for horse serum in prophylaxis, in order to avoid a tendency to anaphylaxis, has been carried out in the Argentine, but in this country, so far as I know, cattle serum is not available.

The prophylactic dose of diphtheria antitoxin is usually 500 units, irrespective of age, and may be given subcutaneously or intramuscularly.

The administration of antitoxin by the mouth, which is still sometimes practised both for prophylactic and therapeutic purposes, is, as I pointed out over twenty-one years ago (1906), absolutely futile, and the attribution of any value to it is due to ignoring the fact that many persons exposed to infection may escape an attack of diphtheria, not only among the medical and nursing staffs of large fever hospitals, but also among the more susceptible population of younger persons. A convincing proof of the uselessness of this mode of administration of antitoxin has recently been furnished by the Schick test, a positive reaction being in no way affected after administration of antitoxin by the mouth, while it is immediately rendered negative by subcutaneous injection (Aviragnet, Lereboullet, and Marie; Lesné, Boutellier, and Longevin). The inefficacy of rectal injection of antitoxin has been proved in the same way (Raymond).

It is generally agreed that prophylactic injection of antitoxin should be confined to children, and that adults should not be so treated, on the grounds that the latter are less susceptible to diphtheria and are more likely to come under treatment early if they do contract the disease, whereas they are more prone to a severe attack of serum sickness.

In hospitals and well-to-do families in private practice where the children can be kept under close observation after exposure to infection, passive immunization need not, in my opinion, be carried out, though I am well aware that it is the practice in some clinics to administer prophylactic injections on a large scale, with or without a preliminary Schick test, on the occurrence of a single case of diphtheria in a children's ward.

ACTIVE IMMUNIZATION.

In contrast with the temporary protection afforded by passive immunization, a more durable and possibly permanent immunity is conferred by active immunization. This method of protection against diphtheria was first introduced in 1913 by von Behring, to whom we are also indebted for diphtheria antitoxin, but it was first used on a large scale by Park and Zingher in the United States, and subsequently on the continent of Europe, and last of all in this country, where its progress has been less rapid than elsewhere, but now appears to be steadily gaining ground. The substance used for injection at first consisted of a standardized mixture of toxin and antitoxin, three subcutaneous injections of which were given in doses of 0.5 to 1 c.cm., with intervals of a week between each dose. The Schick test was then performed to determine whether immunity had been established or not.

* Read in opening a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Cardiff, 1928.

It has recently, however, become the practice to dispense with the preliminary Schick test, especially in public health work, in dealing with children under 6 years of age, owing to the great majority of them being susceptible to diphtheria, and an unnecessary prick is thus avoided. On the other hand, in the case of adults, who are more likely to react severely than children to the immunizing injections, a preliminary Schick test is indispensable. This particularly applies to the nursing staffs of fever hospitals, in a large proportion of which it is now the rule to carry out active immunization of the nurses when they join the staff.

Since the introduction of active immunization of newcomers—it was considered unnecessary to apply the method to the older nurses—the incidence of diphtheria among the nurses at my hospital, though it has never been very high, has shown a slight fall. It must be admitted, however, that attacks of diphtheria occasionally do occur in nurses whose Schick reactions were negative either spontaneously or as the result of active immunization. This occurrence is probably due to the fact that nurses in the course of their duties are exposed to massive doses of virulent infection which succeed in breaking down their natural or acquired immunity, whereas other persons with negative Schick reactions, who are exposed to only slight and occasional infection, escape.

In some hospitals active immunization is made as compulsory as vaccination against small-pox, while in others it is optional. I have adopted a halfway plan of making all nurses who object to active immunization call at my office, and I have found that the disagreeable prospect of an interview with the medical superintendent usually acts as a deterrent to refusal. In addition to its use in protecting nurses, active immunization is also indicated in schools, crèches, orphanages, and other collections of children.

Although no fatal accidents following active immunization have taken place in this country, the local reaction and constitutional disturbance are occasionally sufficiently severe to necessitate the nurse being taken off duty for one or two days. In these circumstances, therefore—namely, occasional failure to protect and possibility of severe reactions—I have hesitated to make active immunization against diphtheria compulsory like vaccination against small-pox, especially as in diphtheria antitoxin we have an infallible remedy which will jugulate the disease if used within the first twenty-four hours; whereas in small-pox there is no treatment, however early it is applied, which will invariably modify its course.

The fatal accidents to which I have alluded have been extraordinarily rare in comparison with the vast number of prophylactic injections given, but have of late acquired an undue prominence. With the exception of the disaster reported by Tsen, Dzen, and Chang, which occurred in China, where the deaths of 5 out of 81 persons injected appear to have been due to a streptococcal contamination of the toxin-antitoxin mixture, the fatalities were caused by diphtheritic intoxication, as at Dallas in Texas,¹ at Baden near Vienna,² and at Moscow.³ Death in such cases occurred within a few days from toxæmia, or two or three weeks later from characteristic diphtheritic paralysis, while cases which recovered had cutaneous necroses at the site of injection or extensive paralysis. In this country, however, as already stated, no fatalities following active immunization have occurred, or at all events have been reported, nor, indeed, is it likely that they will occur in the future, owing to the fact that the toxin in the immunizing mixture has been generally replaced by toxoid—that is, toxin treated with heat and formalin.

Dr. W. H. Park, director of the Research Laboratories of the Department of Health, New York City, has combined the test for determining immunity with prophylactic injection as follows, thus doing away with the necessity for a preliminary Schick test: 1 c.cm. of toxin-antitoxin of the standard degree of incomplete neutrality is injected subcutaneously on the inner side of the arm just above the elbow. On the sixth or seventh day the arm is inspected, and those in whom there is no reaction

are given no further injections. Those who show a slight reaction are given a second injection, and those who give a definite reaction are given two injections. Dr. R. A. O'Brien, whom I recently consulted about this method, kindly supplied me, about six months ago, with a preparation named D.P.I.M. (diphtheria prophylactic immunizing mixture), in which the Schick test was combined with an immunizing mixture for intradermal use. Although satisfactory results have been obtained on guinea-pigs, our experience of the preparation has not been encouraging. Not only were local reactions more severe, but a smaller number of nurses were immunized after the usual number of injections than when the ordinary immunizing preparation was used.

Some French clinicians, such as Lesné, Marquezy, Lemaire, and Monmignat, have recently adopted the nasal route in preference to subcutaneous injection for active immunization, and found that it was possible to convert a positive into a negative Schick reaction by instilling into each nostril three or four drops of pure anatoxin (diphtheria toxin deprived of its toxic properties by the combined action of heat and formalin) for eight consecutive days, followed, after an interval of eight days, by another course of equal duration. Anatoxin, therefore, like adrenaline, can be absorbed into the system from the nostrils, and, if the value of this method is confirmed, intranasal instillation may prove more acceptable, especially to those of a pusillanimous disposition, than subcutaneous injections. The only drawback to the method, as C. Zoeller and G. Ramon have shown, is the impossibility of being certain how much anatoxin has been absorbed, for some may be expelled from the nostrils or pass down the oesophagus. More anatoxin, therefore, must be used, so that intranasal inoculation is not so economical as subcutaneous injection.

TREATMENT.

The treatment of diphtheria may be considered, in order of importance, under the three headings of serum therapy, general measures, and local treatment.

Serum Therapy.

It is the custom in most of the Metropolitan Asylums Board Hospitals to employ comparatively large doses of antitoxin, 4,000 to 8,000 units being given for mild faucial or nasal cases, 12,000 to 16,000 units for moderate attacks, and 24,000 units, repeated if necessary, for severe cases. As regards the route for introduction of antitoxin, unquestionably the best, in my opinion, is the intramuscular, the injection being made on the outer side of the thigh into the body of the vastus externus. The thigh is to be preferred to the gluteal region, not only because there is less risk of injuring important vessels and nerves, but also because the femoral muscles are much more compact and exercise greater pressure on the injected fluid. Intramuscular injection ensures a much more rapid absorption of antitoxin than the subcutaneous method, and is much safer and pleasanter for the patient than intravenous injection, which, as even its most enthusiastic advocates admit, is followed in a large proportion of cases by rigors or shock.

Abscesses at the site of injection, which if proper care be taken should be extremely rare, are less common, in my experience, than after subcutaneous injection, and usually heal up quite as quickly.

It might seem hardly necessary to give utterance to the commonplace remark that we should be guided by the clinical appearances and not by the bacteriological report in the treatment of a case of sore throat, but I still frequently see cases that have been treated at home for "septic tonsillitis" owing to a single negative swab which has probably not been taken with sufficient care, and are sent to hospital only to die when the clinical evidence of diphtheria becomes too glaringly obvious.

While fully convinced of the importance of the early administration of antitoxin—I have never seen a death from diphtheria or severe paralysis when antitoxin had been given on the first day of disease—I cannot too strongly denounce the doctrine which appears still to be widely taught, especially by throat specialists, that antitoxin is of no value after the fifth day of disease. If this doctrine

¹ *Jour. Amer. Med. Assoc.*, 1919, lxxiii, 1778.

² *Klin. Woch.*, 1925, iv, 169.

³ *Bull. Inst. Pasteur*, 1927, xxv, 312.

were consistently acted upon the mortality of diphtheria would be considerably higher than it is at present.

In a series of 3,000 diphtherial patients of whom I was in charge throughout their illnesses no fewer than 539, or 17.9 per cent., were admitted after the fifth day. With the exception of 12 very mild cases all the patients in whom membrane was present in the throat or nose received antitoxin. Of these 19 died—a mortality of only 5.5 per cent. As the great majority of these cases were in children, and every form of the disease was represented, the low mortality cannot be attributed to the patients being adults, among whom the death rate from diphtheria is usually low, nor to the mildness of the attack. In view of the fact that in the pre-antitoxin era, even when cases were brought under treatment at the very onset of the disease, the mortality was never less than 28.8 per cent., and often rose to 50 per cent. or higher, we can only ascribe the low figure of 5.5 per cent. to the use of antitoxin.

It is important to realize, as I pointed out many years ago (1907), that the evolution of diphtheria may be rapid and malignant, so that even enormous doses of antitoxin given on the second day of disease may not avert a fatal issue; or comparatively slow and benign, so that the disease, which may have been in progress for a week, yields rapidly to a small dose of antitoxin without any sequels.

We should, therefore, be guided by clinical rather than chronological considerations in our treatment of diphtheria—the presence of membrane in the throat, nose, or elsewhere, however late in the disease, being an indication for serotherapy. I have seen so many late cases in which my original gloomy prognosis was happily falsified that I am inclined to say of diphtheria as Ricord did of syphilis: "As regards recovery, everything is possible, sometimes even the impossible."

The chief advance in recent times in the treatment of diphtheria is the use of a refined or concentrated serum whereby the incidence of rashes and other unpleasant sequels is reduced to a minimum. Since our employment of this serum at the Western Hospital in April, 1927, the frequency of serum sickness has fallen from about 60 to under 30 per cent. The only serum phenomenon now seen is urticaria, which is often limited to the site of injection, lasts only for a few hours, and is not accompanied by rise of temperature or constitutional disturbance. With the raw or unconcentrated serum not only was urticaria much more frequent, but in about 12 to 15 per cent. of the cases injected a secondary rash, at first amorphous or morbilliform and later circinate, appeared, usually attended by a more or less considerable rise of temperature, pains in the joints or muscles, and a varying degree of cervical adenitis. In a small percentage of cases there was a return of the sore throat, manifested by patches on the tonsils, to which I gave the name many years ago (1906) of "angina redux." Since the refined serum has been employed I have not seen any of these manifestations of the secondary syndrome.

The introduction of this refined serum is a great boon to the patient. Though somewhat more expensive than the unconcentrated antitoxin it is well worth the additional cost. In previous times it not infrequently happened that the patients, especially adults, suffered as much or even more from serum sickness than from an attack of diphtheria.

General Treatment.

Next to early administration of antitoxin the most important principle in the treatment of diphtheria is the enforcement of rest for a period proportionate to the severity of the initial angina. In mild cases rest in bed for the greater part of the time in the recumbent position should continue for three weeks, while in severe cases the period of recumbency should be extended to six weeks, or more if any paralysis is present.

It is doubtful if any drug has the power to modify favourably the course of the disease, though I am inclined to think that adrenaline may be of value in forestalling or combating the suprarenal insufficiency which plays an important part in the syndrome known as cardiac paralysis.

Alcohol was long regarded as an indispensable drug in the treatment of diphtheria, and as such was advocated by such well-known authorities as Jacobi of New York

and Ker of Edinburgh, as well as by many lesser luminaries in the medical firmament. Even now it is still used on a large scale in the acute stage or in convalescence by some pyretologists, who harbour the delusion that alcohol is a cardiac stimulant or is otherwise indispensable.

When I was appointed medical superintendent at the Western Hospital I found that the annual consumption of brandy in the previous year (1925) had been 2,589 oz., most of which had been employed in the treatment of diphtheria. I at once set to work to convince my colleagues that alcohol, so far from being of any value in the disease, was liable to increase the myocardial degeneration initiated by the diphtheritic poison.

The result of my anti-alcoholic campaign was that the amount of brandy ordered on the diet sheets fell from an average of about 30 oz. daily to *nil* without any ill effects, the diphtheria mortality being lower in 1926 (4.53 per cent.) than in the previous year (8.54 per cent.), while in 1927, when no alcohol at all was used in the treatment of the disease, the diphtheria mortality (3.01 per cent.) was lower than in any of the other Metropolitan Asylums Board hospitals, although the type of disease has remained the same during the last three years.

Time does not permit me to deal with the relative merits of tracheotomy and intubation, or to discuss the management of diphtheritic paralysis, about which there is little new to be said. A few remarks, however, may be made, in conclusion, as regards the local treatment of diphtheria. Since the introduction of antitoxin local treatment in the form of syringing, spraying, or gargling has occupied a very secondary position in treatment. In my series of 3,000 cases I have employed local treatment in only 364 cases, or 12.13 per cent. Most of these patients were older children or adults, who welcome any form of local treatment, which young children as a rule resist.

From comparative observations I have found that the average period for the throat to become clean after injection of antitoxin is practically the same, whether local treatment is employed or not.

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RARE COMPLICATIONS OF ACUTE APPENDICITIS.*

BY

R. KNIGHTLEY SMITH, M.R.C.S., L.R.C.P.,

HOUSE-SURGEON, KIDDERMINSTER AND DISTRICT GENERAL HOSPITAL.

THE following cases of appendicitis are of considerable interest and seem to deserve recording. They are noteworthy on account of their extreme rarity, and because they present many unusual features, which increased the difficulty of pre-operative diagnosis.

CASE I.—Acute Appendicitis Accompanying a Perforated Duodenal Ulcer.

A man, aged 35, was admitted to hospital on August 21st, 1927, complaining of abdominal pain and vomiting.

History.—Nine hours before admission the patient was seized with sudden pain in the upper part of the abdomen. The pain started slightly to the right of the mid-line, and passed down the right side of the abdomen into the right iliac fossa. It was sufficiently severe to double him up, and its onset was accompanied by vomiting. The patient had suffered off and on for eighteen years with pain in the upper abdomen, coming on two hours after food and lasting for a variable period. The pain was relieved by taking food. He gave no history of vomiting, and had never been jaundiced; the bowels and micturition had always been normal.

* From a paper read to the Kidderminster Medical Society, April 20th, 1928.