SPECIFIC ANTITOXIN IN THE TREATMENT OF SCARLET FEVER.*

BY

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I WISH to record some of the results which I have had, during the past few months, in the treatment of cases of scarlatina with specific streptococcus antitoxin, and shall confine my remarks to the results in cases treated within the first few days of the disease; not because good effects are only to be looked for in cases treated thus early, but because the results in cases receiving the serum within two or three days of the onset have been so striking as to leave with me no doubt of the very great value of the treatment. In such early cases the attack has been completely aborted, and desquamation and complications prevented, or greatly diminished; so much so that the quarantine time could be reduced by some 50 per cent.

In cases not coming under treatment until the fourth day of the disease or later the results are much more difficult to estimate, and it will require a much longer time—many months—before definite conclusions can be formed regarding the beneficial effects on the general course of the disease, and the power of the serum, when first given comparatively late, to prevent secondary complications and sequelae or to reduce their severity. I shall hope to report more fully at a later date.

Since 1885 it has been known that haemolytic streptococci were to be found in the throats of patients suffering from scarlatina in the early stage. In 1895 Marmorek prepared an antitoxic serum in the horse by injecting cultures of this streptococcus. This antitoxin was used in the treatment of cases, but the results appear to have been indefinite. In 1902 Moser similarly prepared an antitoxin from the use of which he believed he obtained beneficial results, but other observers employing this serum failed to confirm this. In 1905 Jockmann published a review of the work done along these lines, and examined the claims made that the haemolytic streptococcus so frequently found in the throats of scarlatina patients was the causative agent of the disease. He came to the conclusion that a good case had not been made out, and that this streptococcus was not the causative agent but a secondary invader. Work on the subject then lapsed and no important advance appears to have been made for some twelve years.

In 1917 Schultz and Charlton, experimenting with serum from convalescent cases of scarlatina, found that this serum, when injected into the skin of acute cases of the disease, while the rash was well marked, caused complete blanching of the rash in a small area at the seat of injection. They also found that the serum from some healthy individuals produced this result, whereas the serum from cases in the early stage of scarlatina did not possess this power. This was a great step in advance, but was not so recognized at that time. In 1923 Mair,¹ repeating these experiments of Schultz and Charlton, explained this reaction thus:

"Scarlet fever is apparently a general toxæmia and the rash only a manifestation of the toxin uniting with the tissue cells causing a capillary dilatation with swollen papillae. The serum injected neutralizes the toxin in the tissues and causes the disappearance of the rash. The negative reaction of the sera of acute cases of scarlet fever is simply due to the fact that antitoxin has not yet developed."

In 1919 Dochez, Avery, and Lancefield devised a new method for the differentiation of biologic types of haemolytic streptococci. This led to a further study of the haemolytic streptococcus so constantly found in the throats of scarlatina patients. Reports by Dochez and Bliss, Tunnichiff, M. H. Gordon, and Stevens and Dochez led to the conclusion that this haemolytic streptococcus was a specific type.

Drs. George and Gladys Dick succeeded in producing experimental scarlatina in a volunteer by swabbing the throat with a pure culture of a haemolytic streptococcus from a case of scarlatina (1923). It was now established

beyond all reasonable doubt that this haemolytic streptococcus was the specific causative agent of scarlet fever.

The Dicks also demonstrated, in 1924, that Berkefeld filtrates of media in which the specific streptococcus is grown contain a toxin, and that this toxin, in suitable dilution, injected intradermally, produces a positive skin reaction (the Dick test) similar to the Schick test with the diphtheria toxin.

Dochez of New York described, in January, 1924, an antitoxic serum which he had produced in the horse by adopting a most ingenious method. In order to protect the streptococci from the phagocytic action of the leucocytes of the horse he injected liquefied agar subcutaneously into the horse's neck, and, when the agar had cooled and solidified, living *Streptococci scarlatinae* were injected into the agar. Thus protected the organisms survived and produced toxin which was taken up by the blood stream. After a course of immunization of six months the horse was bled and the serum tested in cases of scarlatina.

Employing this antitoxic serum, Blake, Trask, and Lynch obtained very good results in the treatment of cases of scarlatina, a single intramuscular injection of the serum in early cases being followed by prompt disappearance of the rash and symptoms of toxæmia and a very rapid convalescence without complications. They found also that the serum, injected intradermally in cases with early scarlatina rash, caused complete blanching of the rash at the seat of injection (Schultz-Charlton reaction). They also demonstrated that the toxin circulating in the blood of acute cases of scarlatina is completely neutralized within a few hours after the injection of Dochez's serum. They showed this by bleeding the patient immediately before treatment and obtaining positive Dick skin reactions in susceptible individuals, and by again bleeding at frequent short intervals after the injection of Dochez's serum. Even in some very toxic cases the Dick tests were negative as early as four hours after the administration of the serum.

In April, 1924, the Dicks reported the production of an antitoxin in the horse by a different method. They employed for immunization increasing doses of Berkefeld filtrates of media in which the specific streptococcus had been grown. This antitoxin also gave good results. Quite recently Messrs. Parke, Davis and Co. have put on the market an antiscarlatinal serum prepared by immunizing horses with injections of both the living organisms and of toxin. It is claimed that this serum is both antitoxic and bactericidal.

Ferry, Pryer, and Fisher report results in thirty cases of scarlatina treated with antitoxic and antibacterial serum in Detroit. In twenty-two of these the fever and symptoms promptly subsided and recovery was rapid. In five response was somewhat more tardy, but the results were good. In three cases the course of the disease did not appear to be influenced by the serum. Unfortunately the duration of the illness at the time the serum was first administered is not given in any account of this series which I have seen. This, in our experience, is an all-important point.

Last June Dr. Dochez was kind enough to send me a supply of his serum for trial in cases of scarlatina here. It was whole serum and the dose recommended was 30 to 40 c.cm. by intramuscular injection. Later he had sent on to me further supplies of serum prepared, by his method, by Messrs. Eli Lilly and Co., of Indianapolis. This serum was concentrated (by methods similar to those generally employed in preparing diphtheria antitoxin), the dose being reduced at first to 20 c.cm., and in the later supplies to about 10 c.cm. I have also, during the last few weeks, obtained supplies from Messrs. Parke, Davis and Co.; this product also is a concentrated serum.

Belfast has during the past few years experienced extensive outbreaks of scarlatina of fairly severe type. While the case mortality has not been very excessive (in 1,700 cases in Purdysburn Fever Hospital last year it was 3.3 per cent.), the incidence of complications—arthritis, severe adenitis, rhinitis, otitis, etc.—has been high, and the duration of detention in quarantine has been long. Although there have been many mild cases which could be released from isolation after four or five weeks, the average duration of

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illness at the time of discharge from hospital was last year over six weeks. The "return-case" rate (taking a period of forty-two days) was 2.7 per cent. The case mortality in 800 cases in the first six months of this year was 2.1 per cent.

Such was the type of scarlatina in which we were able to test the results of this new treatment. The first supply of serum which I received from Dr. Dochez consisted of twelve bottles of 40 to 45 c.cm. each. I concluded that the best use to make of this for test purposes was to give it to cases of more than average severity who were admitted early in the attack. It was therefore given mainly to patients with intense rash who were not more than three days ill. (Some of it was given to advanced cases of very severe septic type; but that is another story.)

This serum was whole serum (unconcentrated) and the dose recommended by Dr. Dochez was 30 to 40 c.cm., according to severity. It was given intramuscularly. We started with this dose, but the results in the first few cases were so good that we attempted to conserve our very limited supply and to spread it over a larger number. In some cases in young children one bottle was divided between two, and in other instances two bottles were divided among three cases.

Fourteen early cases were thus treated with an average dose of 32 c.cm. The results were good, exceedingly good. In all fourteen cases there was a very rapid disappearance of the rash and of all toxic symptoms. Six were treated on the second day of illness, seven on the third day, and one early on the fourth day. Of the six treated on the second day three showed no desquamation, and three had fine powdery desquamation, only to be found by careful search. One had slightly enlarged cervical glands—they were just palpable—in the third week. There were no other complications. Of the seven cases treated on the third day, two had no desquamation, five had slight desquamation; three had mild cervical adenitis, two had slight joint pains—in one case confined to the shoulders for one day only, the other had pains in several joints for some five days; this patient had a history of having had rheumatic fever two years previously. The one case treated on the fourth day had mild desquamation, but no complications. In all these cases the fever subsided very rapidly. It has been customary in the reports of cases treated with this serum in America to lay stress on the critical fall of temperature; personally, I do not attach very much importance to rapid fall of temperature, as in my experience such changes in the temperature charts are common when any form of serum is used. In thirteen of the cases in this series the temperature had reached normal, and remained there, by the fifth day from the onset; in the remaining case it did not finally come down till the sixth day. As a rule the temperature was down to normal, and stayed there, in twelve to forty-eight hours after the administration of the serum. Three of these fourteen cases developed urticarial serum rashes, but in none did this give rise to any serious discomfort. No attempt was made to discharge these cases from hospital before the ordinary time, as we were anxious to watch them far into convalescence.

I was very greatly impressed by these results and eager to make further tests, but it was several weeks before I was able to secure further supplies. As they came to hand they were used in the same way, and we are now able to obtain the serum in quantity. The results continue good.

Up to the present we have treated 140 cases by this method. Many of the later cases have been discharged from hospital after periods of isolation very much shorter than had ever been possible before. In the last few weeks we have released from isolation over twenty cases whose quarantine time, from the onset of illness, varied from seventeen to twenty-four days. The cases thus early released had, of course, come under treatment very early in the attack.

I shall mention a few cases which may be taken as typical of the series.

CASE I.

A man, aged 29, was admitted on the second day of illness. He had a vivid general rash, very acute throat affection, and the temperature was 103°. He was given 10 c.cm. of concentrated serum. The temperature fell to normal the following day, and so

remained. The rash had completely disappeared in thirty-six hours. The throat symptoms rapidly subsided, but the fauces remained bright red for several days. There was very slight powdery desquamation, confined to the shoulders, on the ninth day, none elsewhere at any time. There were no complications, and he was discharged on the twenty-third day from the onset.

CASE II.

A boy, aged 13, was admitted on the second day with intense rash and very acute throat affection; he was very toxic and delirious, with a temperature of 103.4°. He was then given 10 c.cm., and this dose was repeated some twenty hours later. The symptoms subsided rapidly; the temperature fell to normal on the fifth day, and he had no further fever and no complications. There was slight desquamation on the abdomen only. Convalescence was rapid, and he was discharged on the twenty-first day from the onset.

CASE III.

A child, aged 3, was admitted within twenty-four hours of the first noting of illness. He had then well marked general erythema, and vivid rash with very acute throat affection, and the angular glands were already enlarged. He was given 10 c.cm.; forty-eight hours later there was no trace of rash and only slight redness of the fauces. There was no desquamation at any time and no complications. On the ninth day he had an urticarial serum rash, which was visible for two days. Thereafter he remained well, and he was discharged on the nineteenth day.

We have had several such cases in young children, the type in which it is so common to have throat, nose, and ear complications, necessitating long detention in hospital.

CASE IV.

A junior medical student, aged 18, was admitted on the second day of illness. On the first day he felt slight sore throat on rising in the morning, but attended his classes that day. In the evening he had very sore throat, and severe headache. The following morning he had acute inflammation of the throat and nausea, and the rash was noticed late in the afternoon. He came into hospital that night. Forty-three hours from the first indication of sore throat he was given 10 c.cm. of serum intravenously. He had then very intense deep-coloured erythema, with well marked general rash, very inflamed throat, was moderately toxic, with a temperature of 103°. Two hours after the serum was administered the temperature had risen to 103.6°; but it then fell steadily, and was normal in thirty hours. The erythema had gone, and the rash was much faded twenty-four hours after the serum was injected. Traces of rash and slight pigmentation could be seen for another two days. There was considerable redness of the fauces for five days. He was then feeling quite well. There was no desquamation, no complication, and no serum rash. He remained well, was discharged on the seventeenth day from the onset, and returned to his classes in the university on the eighteenth day. He had passed through a sharp attack of scarlatina and only missed thirteen days' classes. This was the only case in which we have given the serum by the intravenous route; in all others it has been injected intramuscularly.

These results are exceptionally good, but they are typical of those we have had when it has been possible to administer the serum well within the first forty-eight hours of illness. Every hour appears to count, and when the case has advanced into the fourth day or later the effect on the rash and throat symptoms is much more gradual, desquamation is more marked and general, and cervical adenitis, though always mild, has been observed in many cases.

The following may be taken as typical of cases first treated later than the third day.

CASE V.

A girl, aged 6, was given serum on the fourth day of illness; she then showed very intense rash and very acute throat. The temperature fell to normal by the sixth day, but the throat remained very inflamed and angry for a week, desquamation was general and fairly free. There were no complications.

CASE VI.

This patient, a girl aged 11, was sister to Case v, and was admitted at the same time; the attack in her case was of about equal severity, except that the rash was rather more marked; the throat signs were of equal severity, but the duration was one day, or rather more, shorter at the time the serum was injected. In this case the rash disappeared very much more rapidly, the throat cleared up in a couple of days, and there was no sign of desquamation and no complications.

Of the 140 cases who have received this treatment some are quite recent, but 100 are available for review. In this series the incidence of complications has been exceedingly low. Scarlatinal rheumatism has been almost entirely absent, with the one exception already mentioned in a patient who had a history of rheumatic fever two years previously.

There has not been a single case of severe cervical adenitis, and only a small percentage have had angular

glands large enough to be easily palpable. We have not once seen a purulent discharge from the nostrils, but two cases, which both first received the serum on the third day of illness, did develop otorrhoea of mild type. There has not been a case of late nephritis.

I wish again to emphasize that this report deals only with cases which have come under treatment early in the disease.

As the result of the experience I have had with this treatment, I am very hopeful that we have now a remedy which gives promise of great usefulness, and if the estimate we have formed is found to be the general experience we may look for a reduced case mortality, a great reduction in the very severe complications and after-effects of scarlatina, and also, with the cutting down of the necessary quarantine time, we may hope for much relief to the strain which scarlet fever so often puts on the accommodation of isolation hospitals, and for a material reduction in the cost of such institutions. As a prophylactic this new method should prove of great service.

In the preparation of this serum there are at present great difficulties. The fact that the ordinary laboratory animals cannot be made use of to measure the antitoxic value of the serum is a great handicap. The need of the moment is a reliable and simple method of estimating the potency of any particular batch of serum. At present this can only be done in human beings, either by the effect on the intradermal reactions with toxin in healthy susceptible individuals or by the Schultz-Charlton reaction in early cases with scarlatina rash. Even by these methods it must be acknowledged that the estimate which can be formed is very crude. No doubt time will solve the difficulty, but until it is solved there is, I fear, danger that serum of low potency may find its way on to the market. We know that this has occurred with other antitoxic serums.

It would appear that the two essentials in securing maximum results with this method are—serum of high standard, and very early cases.

REFERENCE.
¹ *Lancet*, December 23rd, 1923.

SALIVARY CALCULUS.

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THE occurrence of calculi in the salivary apparatus is well known, although infrequent as compared with the incidence of stone in the biliary and urinary systems. This comparative infrequency, hardly to be termed "rarity," is such that the presence of salivary calculi may be overlooked and the condition escape recognition when the patient is first seen.

In almost all textbooks of surgery mention, more or less detailed, is made of salivary calculi, and it is now possible to formulate a fairly typical syndrome. It happens, however, that patients sometimes do not spontaneously furnish a typical history, and the latter may or may not be elicited by interrogation. In such cases as the last the discovery of calculi is dependent on the surgeon being alive to the possibility of their presence, and keeping in his mind the salient clinical features of the condition.

Clinical Course.

The patient usually complains of pain in the floor of the mouth, associated with a swelling there which appears or increases during mealtimes, at which times the pain also is aggravated. Such a history is almost more than suggestive of obstruction in Wharton's duct, the common situation of a salivary calculus. Should, however, the calculus be in Steno's duct, pain will be experienced in the cheek and swelling may be observed there.

When the stone has existed for some time, and has reached a size sufficient to produce obstruction of the duct, enlargement of the salivary gland concerned may be expected. In the case of the submaxillary there may be a visible swelling below the jaw. Swelling of the gland indicates more or less

inflammation of that organ, and on palpation it is found to be of firm consistence. As with the duct, pain may be experienced in the swollen gland during mealtimes, and helps to differentiate the firm swelling from that of malignant disease of upper cervical lymphatic glands. Further help in the differentiation is obtained by bimanual palpation, which shows the external to be continuous with an intrabuccal swelling in the posterior part of the floor of the mouth.

The patient sometimes complains also of a disagreeable taste in the mouth, in which case a streak of pus will usually be seen exuding from the duct orifice, or further back in the floor of the mouth. The occurrence may or may not be associated with an acute inflammatory exacerbation. If marked inflammation exists the presence of calculus may be very successfully masked.

Inspection of the floor of the mouth in a suspected case may show swelling and redness of the orifice of Wharton's duct, and if a probe introduced into the duct strikes the stone the diagnosis is made certain. Sometimes one end of a lenticular-shaped calculus may protrude from the orifice, the inflamed or ulcerated margin of which grasps the stone. In the absence of such findings, palpation of the floor of the mouth may demonstrate a hard body in the course of the duct. In some cases mobility of the concretion within the dilated duct is a characteristic feature. In another type of case the calculus may be palpated far back and apparently lodged in the substance of the gland.

Spontaneous extrusion of the calculus may occur; more often removal has to be undertaken. This is accomplished by slitting the orifice of the duct, or incising directly over the concretion. In the latter case the duct is steadied by fixation forceps applied immediately posterior to the concretion. When the incision is made pus not infrequently wells out, carrying the stone with it. The calculus may not immediately escape through the incision, in which case I have found Lister's ear-hook of assistance. If the calculus be mobile it sometimes retreats into a loculus, may for long defy the surgeon's efforts, and be dislodged only with great difficulty. In cases where the above measures fail, and in cases where the stone is situated in the gland or in the commencement of the duct and cannot be extracted in the floor of the mouth, extirpation of the submaxillary gland from without is called for. While a comparatively easy operation as a rule, extirpation is sometimes rendered very difficult by inflammatory matting of the parts, and not only may the buccal cavity be opened into, but the lingual nerve may not escape injury.

Physical and Chemical Characters of Calculi.

Of yellowish-white colour, and sometimes of faintly greenish hue, salivary calculi may be spherical, torpedo-shaped, or cylindrical. Their surface may be smooth, but is often finely tuberculated. While usually the calculus is solitary, examples of multiple concretions are occasionally met with. Their composition is made up by mineral salts and animal matter. The salts concerned are variously given by different authors. According to Erichsen,¹ Waterhouse,² Ivor Back,³ and H. Bailey,⁴ they are principally calcium phosphate and carbonate; Butlin and Spencer⁵ say chiefly calcium phosphate with some carbonate; Syme⁶ mentions calcium phosphate alone, and Pearce Gould⁷ calcium phosphate and some ammonio-magnesium phosphate. Analysis was made in four of my cases (vide infra), and showed either phosphates alone or along with mere traces of carbonate.

Such salts as are found in the calculi occur also in the saliva, the composition of which is as follows: calcium phosphate and carbonate, sodium carbonate, potassium sulphate, and chlorides of sodium and potassium; carbonates are particularly abundant; mucin is abundant in submaxillary and sublingual, and absent in parotid, saliva (Howell,⁸ with whom Flack and Hill⁹ in the main agree).

Etiology.

The calculi are the result of the precipitation of the salts of the saliva. The exciting cause of the precipitation is not definitely known. Butlin and Spencer (loc. cit.) think that calculus formation is apparently connected with the presence of a plug of inspissated mucus. The same view is elaborated