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SCARLET FEVER.*

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INFORMATION concerning scarlet fever has come from two sources: clinical observation and laboratory investigation.

Although descriptions of diseases characterised by rashes are found in the earliest medical writings, our knowledge of scarlet fever as a disease entity dates from the time of Sydenham, who, in 1675, differentiated the disease from measles and gave to it the name "Febris Scarlatina."

The contagious nature of scarlet fever was early established, and it was learned that one attack usually confers a lasting immunity, but that relapses and second attacks may occur.

Clinical experience taught that the contagiousness of scarlet fever lasts beyond the acute stage, being more nearly coincident with the time required for desquamation.

It was learned that survival of the acute stage of scarlet fever does not ensure against death from complications or sequelæ.

It was noted that some persons go through life without having a recognised attack of scarlet fever despite repeated exposure to the contagion.

The disease was found to vary greatly in severity in the various epidemics and in different individuals in the same epidemic.

The fact that discharges are contagious became accepted.

The sudden onset with vomiting, diarrhœa, high fever, and in the more severe cases, coma or delirium, were recognised as evidence of intoxication and, because of them, clinicians came to speak of the "poison" of scarlet fever and, later, of the "toxic" forms of the disease.

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Scarlet fever in infants was recognised as sufficiently rare to justify reporting, and the medical literature from the time of Sydenham to the present contains numerous descriptions of scarlet fever in infants and even of intra-uterine scarlet fever.

Many references are also found to the importance of the puerperal uterus and of wounds as area of infection, resulting in puerperal or surgical scarlet fever.

Thus by the end of the eighteenth century clinical knowledge of scarlet fever was well developed and important facts of practical value were established.

At this time, Jenner's work on smallpox vaccination stimulated those interested in scarlet fever to attempt vaccination against this disease in the hope of producing a mild form of scarlet fever which would protect against more severe attacks. In 1806 Becker, a German physician, published a book describing various methods of inoculation then in use, most of which originated in England. He especially recommended obtaining blood from a cut in the skin of a scarlet fever patient and rubbing it into scarifications on the arms of persons to be protected. Other materials used in a similar way were: pulverised skin scales from desquamating cases, linen threads moistened in tears or saliva, and exudates from the throats of scarlet fever patients.

These methods proved impractical and were soon abandoned. They did not confer immunity without producing an attack of scarlet fever, and when the disease did result, it was often severe.

In the latter part of the nineteenth century, the rapid development of bacteriology stimulated endeavours to find the causative organism of scarlet fever, and a vast literature resulted which time does not permit reviewing here.

Organisms of streptococcus morphology were found as early as 1869 by Hallier and subsequently a variety of organisms, including protozoa, were described as the cause of scarlet fever.

It was not until 1903 that the work of Schottmueller enabled bacteriologists to differentiate hæmolysing streptococci from those which produce green on blood. Following Schottmueller's work, it was learned that it is the hæmolytic type which predominates in erysipelas, puerperal sepsis, pyogenic infections, septic sore throat, and scarlet fever.

The association of streptococci with scarlet fever led some scientists to the opinion that they were the cause of the disease.

But attempts at treatment with antistreptococcus serums, including Moser's of 1902, failed. Streptococcus vaccines, of which Gabritchewski's was the most extensively tried, likewise failed in both the prevention and treatment.

All attempts to produce experimental scarlet fever were unsuccessful. These experiences, together with the finding of streptococci in other diseases, resulted in the view that scarlet fever was caused by an unknown organism or filterable virus and that streptococci were important but secondary invaders.

As a whole, reports of laboratory investigations in scarlet fever, in contrast to results of clinical observations, proved to be confusing when they were not actually misleading.

Thus in 1912, when we began work on scarlet fever, two centuries after Sydenham, the etiology of the disease was still unknown.

Experimental scarlet fever had not been produced. After several years of unsuccessful attempts to obtain acceptable experimental scarlet fever in animals, using a variety of organisms and materials, we concluded that laboratory animals are not susceptible and that to determine the causative organism, it would be necessary to inoculate human volunteers.

In 1923 we reported the successful production of scarlet fever in human volunteers. The experimental disease was produced by swabbing the throat with pure cultures of hæmolytic streptococci isolated from typical cases of scarlet fever. By suitable experiments we were able to exclude a filterable virus as the cause of the experimental disease. We succeeded in meeting all the requirements of Koch's laws, and thus established a specific hæmolytic streptococcus as the etiologic organism of scarlet fever.

This work was subsequently confirmed by Nicolle, Conseil and Durand of the Pasteur Institute in Tunis, and by Toyoda, Futago, and Okamoto in Manchuria. Both groups of workers were able to repeat the experiments in which scarlet fever was produced by inoculation with pure cultures of hæmolytic streptococci and excluded a filterable virus as a cause of the experimental disease.

Since hæmolytic streptococci are found in the throats of scarlet fever patients but are seldom present in the blood stream of uncomplicated cases, it is evident that the rash is not produced by direct action of the streptococcus on the skin. This had suggested to us that the hæmolytic streptococcus

growing in the throat might produce a soluble substance which in turn is responsible for the rash.

Sterile filtrates were prepared from cultures of the organisms which had produced experimental scarlet fever. When these filtrates were injected intradermally in proper dilution, they caused localised areas of erythema in 41·6 per cent. of persons giving no history of scarlet fever; while all of the convalescent scarlet fever patients tested showed negative or only slightly positive reactions.

In persons who showed positive reactions, the effect of the filtrate was inhibited by serum from convalescent scarlet fever patients mixed with the filtrate before it was injected, or by large amounts of convalescent scarlet fever serum injected intramuscularly before the skin test was made.

It was found that this skin reaction which was positive before an attack of scarlet fever, was negative during convalescence.

When some of the persons with positive skin reactions received injections of larger amounts of the sterile filtrate, they developed nausea, vomiting, fever, and a generalised scarlatinal rash. Following this, the reaction of the skin to the filtrate was modified or negative, and the blood serum of these persons was found to have acquired the property of neutralising the action of the filtrate, similar to the neutralising power of convalescent scarlet fever serum.

When graduated doses of the filtrate were injected into horses, the serum of these animals likewise acquired the property of neutralising the filtrate *in vitro*.

The negative skin reactions in convalescent patients; neutralisation of the filtrate by convalescent serum; the occurrence of scarlatinal rashes accompanied by other symptoms characteristic of scarlet fever following injection of the sterile filtrate; the short interval between injection of filtrate and beginning of the reaction (about four hours as compared with an incubation period of forty-eight hours in experimental scarlet fever); rapid disappearance of the symptoms; failure of the filtrate to produce the disease itself in persons who subsequently developed scarlet fever on inoculation with living streptococcus—indicated that the action of the filtrate is due to a soluble toxic substance specific for scarlet fever and not to a filterable virus.

Neutralisation of this toxic substance by scarlet fever convalescent serum, and by the serum of persons immunised

by graduated doses of the filtrate; specific neutralisation *in vitro* of the toxic substance by the serum of horses immunised to the filtrate; and the thermolability—proved that the substance is a true toxin capable of inducing the formation of antitoxin.

It had been thought that true toxins were concerned in comparatively few diseases such as diphtheria, tetanus, botulism, and some forms of dysentery, all of which are caused by bacilli. The manufacture of soluble toxin by streptococci was a new conception. It explained the toxæmia and the lasting immunity which had been considered incompatible with a streptococcus origin.

Scarlet fever toxin and the corresponding antitoxin have furnished the means of controlling the disease through the development of:—

First.—A method of identifying scarlet fever streptococci through neutralisation of their toxin by the specific antitoxin.

Second.—Control of quarantine by means of cultures on blood agar plates.

Third.—A skin test by means of which it is possible within twenty-four hours to determine which individuals in a group are susceptible to the disease.

Fourth.—A method of actively immunising susceptible persons.

Fifth.—A specific scarlet fever antitoxin, useful in the treatment, prevention, and diagnosis of the disease.

The discovery of scarlet fever toxin opened a new field for investigation in which many workers recently have been engaged with the result that soluble toxins produced by hæmolytic streptococci concerned in various diseases have been described, and in some instances the corresponding antitoxins have been produced. While it is not yet possible to determine what the final status of the various toxins and antitoxins will be, it seems to be established that the hæmolytic streptococci found in erysipelas, septic sore throat, and at least some of those concerned in puerperal sepsis are capable of elaborating soluble toxin. The nature of these toxins is a matter of active interest at present.

Different strains of scarlet fever streptococci vary considerably in the potency of toxin yielded. However, the toxin produced by scarlet fever streptococci is of much higher potency than toxins obtained from streptococci found in erysipelas,

septic sore throat, and non-scarlatinal puerperal sepsis. The weakness of these non-scarlatinal toxins makes study of their specificity technically difficult because they must be used in low dilutions containing relatively high amounts of foreign proteins which in themselves tend to cause confusing skin reactions. This necessitates the use of medium containing a minimum amount of foreign protein. Other points to be kept in mind in the study of streptococcus toxins are :—

First.—The employment of serum containing only one kind of antitoxin. It should be remembered that hæmolytic streptococcus infections are common both in animals and in man; consequently a convalescent human serum or an artificially produced antitoxic serum may contain more than one kind of antitoxin.

Second.—Preliminary standardisation of both toxin and antitoxin. This is necessary because the neutralisation reaction is quantitative as well as qualitative.

Third.—Adequate control tests to eliminate errors due to reactions caused by protein in the medium or in the serum employed as antitoxin.

Fourth.—Use of only those individuals as test subjects who are known to be susceptible to the toxins under investigation.

In a series of experiments, arranged in accordance with these considerations and extending over three years, we were able to demonstrate that the soluble toxins produced by scarlet fever streptococci and by erysipelas streptococci are specific and distinct. These results are in accord with conclusions derived from clinical experience in the two diseases.

In the application of scarlet fever toxin to control of the disease in human beings one should be certain that the toxin is derived from strains specific for scarlet fever; that it is highly potent and accurately standardised; also that it contains no animal serum or excessive amounts of other proteins. Slight changes in hydrogen ion concentration cause deterioration of the toxin. To avoid this, it is necessary to use non-soluble glass ware, pure, neutral gum rubber, and chemicals of the highest purity.

Dilute solutions of the toxin are employed to determine susceptibility to scarlet fever. The toxin is first carefully standardised on human beings; for laboratory animals are so insusceptible as to be useless for this purpose.

Scarlet Fever

The technic of the skin test for susceptibility to scarlet fever is exacting. Among the more common sources of error are: inadequate syringes and needles; attempts to sterilise the syringes and needles with alcohol which precipitates the minute amount of toxin in the skin test solution; dilution of the toxin with water left in the syringe and needles after boiling; sterilisation in alkaline tap water instead of distilled water; estimation of the amount of skin test solution injected by the size of the wheal produced instead of accurate measurement by graduations on the syringe; subcutaneous instead of intracutaneous injection, and failure to observe the reaction between twenty and twenty-four hours after the test is made. Slightly positive reactions are frequently interpreted as negative. This tendency may be due to familiarity with the Schick test, which is usually interpreted as negative unless indurated. Scarlet fever toxin does not cause induration. When induration is present, it is usually the result of infection from the skin or contaminated material, or it may be due to an excessive amount of protein in the toxin solution.

In making the skin test, the exact dose is injected intradermally on the flexor surface of the forearm at the junction of the upper and middle thirds. The reaction should be observed in a bright light, twenty to twenty-four hours after the test is made. Observations made later than twenty-four hours are not reliable. The slightest flush or reddening, no matter how faint the colour, constitutes a positive reaction, if it measures as much as 10 mm. in any diameter. It is to be remembered that the test is one for susceptibility to scarlet fever and is not applicable to diagnosis of the disease.

The reliability of the skin test in determining susceptibility to scarlet fever is accepted. Our own experience of the past ten years comprises 24,000 persons having spontaneously negative reactions, who have passed through one epidemic and some through several epidemics without contracting scarlet fever.

The most severe test of the reliability of the skin test is found in a group of more than 4000 pupil nurses and internes with spontaneously negative skin tests, who were allowed to go on duty in contagious disease wards without immunisation. Despite long and intimate exposure none of this group contracted scarlet fever. Re-tests made at intervals of three, four, and six years in spontaneously immune groups show that the

skin test remains negative except in new-born infants, who frequently show negative skin reactions which become positive during the first year of life.

The incidence of immunity to scarlet fever after early infancy depends on conditions that favour exposure to the disease. Immunity is not related to age or sex except indirectly as these factors influence the frequency of contact with other people. The most important factor in the spontaneous development of immunity is crowding, which favours the transfer of contagion and immunisation through infection. Figures showing the incidence of susceptibility to scarlet fever in one group do not give an idea of what the incidence of susceptibility in another group might be, unless the living conditions are practically the same. In an over-crowded institution, the incidence of susceptibility may be as low as 10 per cent., and in rural or suburban groups it may be as high as 85 per cent.

In a series of skin tests, it will be found that the positive reactions show all graduations from small areas of faint colour to intensely red reactions 3 to 5 cm. in diameter. These differences in the intensity and size of the skin reactions correspond to differences in degree of susceptibility, and partly explain the great variation in severity of scarlet fever. The intermediate stages of the reaction also indicate that in many persons immunity to scarlet fever is acquired gradually through repeated infections with the streptococci of scarlet fever without the development of a typical attack of the disease. It has been learned that one attack of scarlet fever sore throat does not necessarily confer complete immunity, but typical attacks of scarlet fever usually do result in complete immunity, as indicated by negative skin reactions in patients convalescent from scarlet fever and by the comparative infrequency of second attacks.

Persons who are susceptible to scarlet fever may be immunised by means of subcutaneous injections of graduated doses of sterile scarlet fever toxin. The dosage should be correctly graduated, so as to give no harmful reactions, yet confer adequate immunity. The efficacy of this method of protecting against scarlet fever has been confirmed to varying degrees depending on the dosage employed by the different observers.

In our experience, active immunisation with graduated doses of sterile scarlet fever toxin in 13,000 susceptible persons

caused no injury in any instance. In three institutions, urine analyses were made before, during, and after immunisation. There was no evidence of nephritis caused by the immunisation. Some persons who had nephritis were immunised without causing an exacerbation of the condition.

In a large series, including highly susceptible persons, general reactions may be expected after each dose in about 10 per cent. But this 10 per cent. is not composed of the same individuals after the different doses. The most highly susceptible persons usually react more strongly on the first doses; others may not have any reactions until the fourth or fifth dose is given. As a rule, reactions after the last and largest dose are fewer and milder than after the smaller first doses. The immunising doses should be accurately graduated and it is important to give them in the proper sequence in order to avoid unnecessarily severe reactions. But mistakes have been made in which the last dose has been injected as the first dose and no fatalities have occurred. Experimentally, we have injected as much as 20 c.c. of undiluted toxin containing nearly 1,000,000 skin test doses, without causing injury and without producing nephritis in human beings.

The doses of sterile toxin for active immunisation should be graduated, beginning with 500 skin test doses in the first injection and increasing to 80,000 or 100,000 skin test doses in the last. The injections are made subcutaneously at intervals of one week. If the full amount is given in each dose, the five doses may be counted on to immunise completely 95 per cent. of susceptible persons, and to modify considerably the susceptibility of the rest. Two weeks after the last dose is given, another skin test is made, using 0·1 c.c. of the skin test solution or one skin test dose on the right arm, and 0·2 c.c., or two skin test doses, on the left arm. If the reaction on either arm is positive, the fifth dose is repeated.

Unless the immunisation is carried to the point of a negative skin reaction, complete protection against scarlet fever can not be expected, although the severity of a subsequent attack would be modified by the partial immunisation.

The duration of active immunity, as well as the degree of immunity, depends on the amount of toxin injected. Re-tests made at intervals of one, two, three, five and six years indicate that more than 90 per cent. of those immunised to the point of an entirely negative skin reaction retain their immunity.

Between 5 and 9 per cent. slip back and require a second immunisation.

Scarlet fever antitoxin is obtained from the blood of horses which have received gradually increasing doses of toxin over a period of several months. The serum is separated, aged, refined and concentrated. The incidence of serum reactions following the administration of scarlet fever antitoxin is slightly less than following the administration of other antitoxins, due probably to greater care in preparation.

The potency of scarlet fever antitoxin is determined by its capacity to neutralise the toxin. One neutralising unit of scarlet fever antitoxin is the amount sufficient to neutralise one skin test dose of the toxin and hold it in combination at least forty-eight hours.

The initial therapeutic dose of antitoxin should contain at least 300,000 neutralising units and the prophylactic dose should consist of at least 100,000 neutralising units. Smaller prophylactic doses do not always suffice to protect against the sore throat, although they may prevent the development of the rash, while the larger prophylactic dose prevents the development of scarlatinal angina as well as the rash and other manifestations of scarlet fever.

Scarlet fever antitoxin is injected intramuscularly in prophylactic doses to confer a rapid, passive immunity on susceptible persons who have recently been exposed. Since the immunity thus conferred does not last more than ten days to two weeks, active immunisation with the toxin should be started one week after the prophylactic dose of antitoxin is administered. Skin tests should be made to determine which individuals are susceptible and in need of protection and, if possible, nose and throat cultures should be made on blood agar plates to learn which of the susceptibles are infected.

It is advisable to give scarlet fever antitoxin even in mild cases, because it is known that complications are apt to occur in mild as well as in more severe forms of the disease. If the attack is severe and the patient very toxic, two therapeutic doses of antitoxin should be given at once, and more after twelve hours if indicated. In puerperal scarlet fever even more antitoxin is required.

Scarlet fever antitoxin is also employed for the diagnosis of doubtful rashes, 0·2 c.c. of scarlet fever antitoxin being injected intradermally in the centre of a large area where the

rash is brightest, preferably on the abdomen or chest. The reaction is observed eighteen to twenty-four hours later. A positive reaction consists of blanching of the rash in a zone surrounding the central red spot where the injection was made. The reading should be made while standing several feet from the patient. The rash of German measles and other non-scarlatinal rashes are not blanched by scarlet fever antitoxin.

Given early and in adequate dosage, scarlet fever antitoxin gives brilliant results. The patient sometimes recovers so rapidly that the attending physician may wonder if he could have been mistaken in the diagnosis. The longer the patient goes without antitoxin, the less he benefits from the antitoxin when it is given. Reports as to the effect of scarlet fever antitoxin in reducing complications are sometimes conflicting, due to delay in administering it or the use of poor preparations. Most scarlet fever antitoxin available in Europe is not standardised and is considerably weaker than the best American product.

Scarlet fever patients in hospitals do not furnish the most favourable material for determining the therapeutic value of antitoxin because they are seen later in the disease than patients treated in their homes. But even with the delay in such cases, it has been shown that scarlet fever antitoxin reduces the number and the severity of complications and lowers the mortality. In a comparison of results in 967 more severe cases treated with scarlet fever antitoxin in the Durand Hospital with the outcome in 1421 cases that appeared less severe when admitted to the hospital, it was found that mastoiditis occurred three times as frequently in the control series as in the antitoxin series; the incidence of post-scarlatinal nephritis in the control series was four times that in the antitoxin series; and despite the milder appearance at the onset, the mortality in the control series was twice that in the antitoxin series.

It is not possible to estimate accurately how many cases of scarlet fever are prevented by administration of scarlet fever antitoxin prophylactically, because susceptible persons exposed to scarlet fever would not necessarily develop the disease. It can only be said that cases of scarlet fever have not occurred within ten days after administration of prophylactic doses of antitoxin, while numerous cases have developed in the same epidemics in contacts not protected by either active immunisation with the toxin or passive immunisation with prophylactic doses of the antitoxin.

There is perhaps a tendency to be too complaisant regarding epidemics of *mild* scarlet fever.

While the frequence of complications is recognised, the lasting injuries resulting from them are not fully appreciated. That complications are not confined to the severe cases is shown by observations in a series of 743 cases of scarlet fever of only moderate severity. Otitis media occurred in 15 per cent., nephritis in 4·7 per cent., cervical or peritonsillar abscess in 3 per cent., and multiple arthritis in 12 per cent.

In 1897 Weissbecker treated a number of diseases, including scarlet fever, by injections of serum obtained by bleeding patients recovered from the diseases. The results were not impressive and until the work of Reiss and Jungmann, it received little attention. At this time larger amounts of serum were injected with beneficial results and, when used in adequate amounts, convalescent serum is a distinct benefit in the treatment of scarlet fever.

The convalescent serum has the advantage of being free from any of the dangers of serum reactions, but its antitoxin content is, at best, only about one-hundredth that of a good scarlet fever antitoxin, so that it is necessary to inject large volumes of convalescent serum to obtain results as striking as those following injection of 10 to 15 c.c. of the commercial antitoxin.

To control an epidemic it is necessary to employ all of the measures described. Under ordinary conditions, not more than 10 per cent. of those who come in contact with patients having scarlet fever become infected, but in institutions where the inmates are in contact with one another during most of the twenty-four hours, more than 50 per cent. may become infected during a prolonged epidemic, and it may be expected that eventually most of those who are susceptible will develop scarlet fever in some form. Conditions in institutions in which the disease is epidemic are favourable for determining the efficacy of active immunisation in controlling scarlet fever. A number of such institutions have been under our observation during the last seven years. Skin tests were made on every one, and those who were found susceptible were immunised with graduated doses of toxin. Among 12,584 susceptible persons thus immunised in institutions where scarlet fever was epidemic, no case of scarlet fever occurred. Controls were furnished by typical cases of scarlet fever developing in newly

admitted persons who had not been tested and immunised before they were introduced into the infected community, and by cases of scarlet fever in teachers and attendants who refused immunisation.

An opportunity to study the results of active immunisation was also found in 3000 susceptible nurses and internes immunised before they began work in hospitals for patients with contagious diseases. These artificially immunised persons had the same prolonged and intimate exposure to scarlet fever that the naturally immune nurses and internes had. None contracted the disease. Controls in this group were furnished by thirty-seven cases of scarlet fever in nurses and internes who entered before they had been tested for susceptibility or who were known to have positive skin reactions and had not been immunised.

Since persons who are immune to scarlet fever do not require protection, the administration of prophylactic doses of scarlet fever antitoxin to all persons who come in contact with cases of scarlet fever is not justified. If it is not possible to make skin tests and nose and throat cultures on blood agar plates to determine which of these persons need antitoxin, it is better to watch all of them closely and give a therapeutic dose of antitoxin on the development of any symptoms suggestive of scarlet fever.

When it is possible to make skin tests and cultures and to establish quarantine, separating infected from non-infected persons, active immunisation of non-infected susceptible persons with graduated toxin injections may be started at once, and prophylactic doses of scarlet fever antitoxin may be given to the persons who are both susceptible and infected.

By means of nose and throat cultures on blood agar plates, skin tests for susceptibility, active immunisation of susceptible persons with the toxin and the use of antitoxin prophylactically in infected susceptibles, it is possible, in a group small enough to test and culture in one day, to bring an epidemic of scarlet fever under control in forty-eight hours.

In concluding, I wish to emphasise that in scarlet fever, as it occurs spontaneously as well as in the artificially produced immunity obtained by injecting toxin or in treatment by administration of antitoxin, there is a *quantitative* element which cannot be left out of consideration if one is to obtain the best results.