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ETIOLOGY OF SCARLET FEVER *

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SCARLET FEVER is in all probability a very old disease. The regions in which the malady originally arose are a matter of uncertainty. There are some who believe that the Plague at Athens was a malignant form of scarlet fever, an interesting assumption in view of the present relatively low case fatality and the ominous variability in severity of outbreaks in the past. Fairly accurate descriptive records of scarlet fever appear in the literature as early as the middle of the sixteenth century and recur with increasing frequency and definiteness up to the time of Sydenham. For many years the disease was confused with measles, erysipelas, diphtheria and certain septic processes. Sydenham, who first employed the name scarlet fever, clearly differentiated it from measles by his careful description of the disease as it appeared in London from 1661 to 1675, and laid the foundation of an accurate knowledge of its special characters. In spite of this valuable contribution, the existing confusion did not disappear, and many physicians still confounded it with diphtheria and certain septic anginas. With the increasing volume of medical literature and better facilities for the communication of ideas, scarlet fever became more and more clearly defined as a clinical entity. Confusion, however, with diphtheria frequently occurred, even down to the times of accurate diagnosis by means of bacteriological methods. In fact, even today the inability to differentiate scarlet fever from certain septic conditions of the throat, associated with erythematous rashes, continues to plague the mind of the diagnostician. In spite of these diagnostic difficulties clinical differentiation of scarlet fever from other exanthemata has been possible for a long enough

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period of time to determine clearly its contagious nature and to permit illuminating epidemiological and clinical studies.

The contagious element in scarlet fever is probably always derived from a previous case. In most instances it is taken directly into the mouth or nasopharynx by the inhalation of air charged with minute droplets of saliva or mucous projected from the mouth or nose of the infected individual. Other important sources of contagion are the purulent discharges from infected paranasal sinuses, from suppurative inflammation of the middle ear and lymph glands, secondary conditions that constitute the most frequent and distressing complications of the disease. There is much evidence to support the view that the causative organism survives in the dry state in a virulent form for long periods of time. Contamination, therefore, of clothing or personal articles of any kind with infective matter may serve as a means of conveying scarlet fever. Formerly the belief was quite prevalent that flakes of skin given off during the period of desquamation were the most important vehicle of the contagion, and quarantine regulations were roughly founded on time periods corresponding with the duration of the desquamative stage. Current opinion holds that the contagious element is not present in the skin in the late stages of scarlet fever, a somewhat curious fact, inasmuch as the rash is the most distinctive clinical manifestation of the disease. The rôle of the healthy carrier in spreading scarlatina is undoubtedly of great importance but determined accurately as yet in only a very few instances because of the uncertainty concerning the etiological agent. That such types of carriers do exist there can be no doubt, and Bliss [1] has been able to trace a small epidemic of scarlet fever to such a source. Another interesting means of the wide dissemination of scarlet fever is an infected milk supply and numerous undoubted outbreaks have arisen from the consumption of contaminated milk. The clinical and epidemiological evidence, therefore, that has been collected indicates that the causative agent of scarlet fever is present in the throat secretions and the discharges from suppurative foci in patients throughout the illness, and for a considerable period of time during con-

valescence. It resists exposure to light, and in the dry state may retain its infectivity for many months. Healthy carriers and atypical attacks of the disease are not an infrequent occurrence. In all probability the udder of the cow may become infected with the specific virus, and the milk obtained from this animal may serve as a vehicle of infection.

Notwithstanding these excellent clinical and epidemiological studies which have ensured the easy recognition of typical attacks of the disease, and which have furnished the essential data for useful quarantine regulations, the causative organism of scarlet fever has remained unknown. Experimental studies have been published from time to time, suggesting that the infective agent belongs to one or other of the principal groups of microörganisms, such as the pathogenic bacteria, protozoa, and the so-called ultramicroscopic viruses. As a bacterial cause, Streptococcus hæmolyticus has aroused much interest and stimulated more or less continuous investigation because of its constant association both with the uncomplicated and complicated forms of the disease. Certain observers have discovered inclusion bodies in leucocytes and in epidermal cells which they have thought indicative of a protozoan cause for scarlet fever. Finally, scientific opinion seized upon those mysterious living bodies commonly designated as filterable viruses as the most probable cause of the disease. This latter view has become most widely accepted and is the usual etiology assigned in text books in spite of the fact that no real evidence has ever been produced to show that any such microörganism exists either in the throat secretions, tissues or blood of an individual suffering from scarlatina.

Both Mallory [2] and Döhle [3] have made the suggestion that scarlet fever may be due to a protozoan infection. In 1904 Mallory observed in four cases of scarlet fever certain bodies whose varying morphology strongly suggested that they might have been stages in the development cycle of a protozoan. They occurred in and between the epithelial cells of the epidermis and free in the superficial lymph vessels and spaces of the corium. They formed a series of bodies including definite rosettes, which

closely resembled those seen in the asexual development of the malarial parasite. There were also certain coarsely reticulated forms which he thought might represent stages in sporogony. Mallory was of the opinion personally that these bodies were protozoa and bore an etiological relationship to scarlet fever, but he did not regard their significance as established. Confirmatory observations were subsequently made by Duval,[4] Bernhardt[5] and v. Prowaçek.[6] Similar bodies, however, were later found by Field[7] in other conditions and they finally came to be looked upon as peculiar products of cell degeneration and not as living forms with a specific relationship to scarlet fever.

In 1912 Döhlé, on examining the blood smears from thirty cases of scarlet fever, found within the cytoplasm of the neutrophilic polynuclear leucocytes multiform inclusion bodies. These inclusions were present in a large percentage of all leucocytes and by special methods of staining revealed themselves as intermediate in intensity between nucleus and cytoplasm. In a later communication certain of these inclusions are designated as "Spirochæta scarlatinæ," and are assigned both diagnostic and prognostic importance. Although numerous observers confirmed Döhlé's observations on the presence of leucocytic inclusion bodies, further study revealed the fact that they are present in practically all febrile conditions, in chronic pyogenic infections without fever, in certain severe injuries, and occasionally in normal human beings. In all likelihood they result from nuclear degeneration not infrequently observed in septic states and have no specific bearing on the etiology of scarlatina. The evidence offered in favor of the protozoan origin of scarlet fever has never stood the test of close scrutiny.

The belief that scarlet fever is due to an unknown virus, probably of filtrable character, is based largely upon the results of attempts to communicate the disease experimentally to animals. A number of observers have reported scarlatina-like manifestations in monkeys inoculated with infective material from active human cases of the disease. Among these observations the most interesting are those of Levaditi, Landsteiner and Prasek,[8] who, by the inoculation of anthropoid apes, seem to have pro-

duced what in all likelihood was true scarlatina. Exudate from the throats of individuals with scarlet fever was rubbed into the tonsils of apes and defibrinated blood injected subcutaneously, and in one instance material from a suppurating lymph gland. The animals, after an incubation period of about three days, are described as having a typical angina with characteristic exudate, enlargement of the follicles of the tongue, a generalized exanthem resembling that of scarlet fever, and in certain instances when the animals recovered desquamation of the skin. There was also present the characteristic lymphoid hyperplasia, and the histological lesions in the skin resembled those seen in scarlet fever. In all the animals presenting such a picture S. hæmolyticus was present, either in the blood or in the local lesions in the throat. Levaditi, Landsteiner and Prasek, however, did not think that streptococcus was accountable for the manifestations, inasmuch as when pure cultures of this organism were obtained from the infected animals or from human beings and inoculated into fresh apes, the phenomenon described could not be reproduced. They do not state that the organism of scarlet fever is a filtrable virus, but simply say that it is of unknown characteristics. Cantacuzene [9] and Bernhardt [10] claim to have induced a similar series of phenomena by the inoculation of monkeys of a lower order with human material. Levaditi, Landsteiner and Prasek failed to produce in a large series of lower monkeys the disease syndrome manifested by the apes, nor were subsequent investigators more successful in confirming the observations of Cantacuzene and of Bernhardt. From the failure to discover an organism of known characteristics, rather than from any positive evidence has grown the belief so generally held that the etiological agent of scarlatina is an ultramicroscopic virus.

During the many years that investigators have searched for the causative agent of scarlet fever, and with the varying emphasis attached to one or another species of parasite from time to time, the constant relationship to this disease of one organism, S. hæmolyticus has become more and more significant. As early as 1885 Crook [11] reported the presence of streptococcus in the blood and organs of individuals dying of scarlet fever.

Loeffler,[12] in addition, found this organism to be present in certain types of necrotic angina associated with scarlet fever and was furthermore successful in isolating the germ in pure culture. At this time Klein [13] likewise isolated a streptococcus from the tissues of patients with scarlatina, which he named Streptococcus scarlatinæ. In 1885 the latter observer, while investigating an outbreak of fever among certain cows belonging to a farm at Hendon, England, isolated from ulcerative lesions of the udders and from certain viscera, a streptococcus which he considered to be identical with Streptococcus scarlatinæ. This observation was not only of great interest but also of very great importance, because the milk obtained from the infected cows was shown to have been consumed by persons who subsequently developed scarlet fever. These early observations of the frequent relationship of streptococcus to scarlatina were soon confirmed by many students of the disease in different parts of the world. In 1900 Baginsky and Sommerfeld [14] reported the constant presence of streptococcus in the throat during the characteristic angina in seven hundred cases of scarlet fever. They also found this organism frequently in the blood, bone marrow and internal organs of patients dying of this disease. Other observers found streptococcus in the blood of fatal cases of scarlet fever in as many as 70 per cent. of the individuals studied. Hektoen,[15] furthermore, found the organism in the blood in 12 per cent. of patients during life, and his observations are of especial interest in that they indicate that the usual bad prognostic import of this phenomenon does not necessarily hold for scarlet fever.

In addition to the presence of streptococcus in the throat and blood of individuals with scarlet fever, this organism has also been proven to be the most frequent cause of the septic complications of the disease. Many times in septic foci streptococcus has been found in pure culture, and it is an old observation that convalescent individuals with discharging suppurative lesions are especially likely to give rise to return cases of scarlet fever, showing that in such lesions the causative virus persists in an active form for long periods of time.

Such widespread and constant association of S. hæmolyticus

with scarlet fever has led some investigators to propose the view that streptococcus is the etiological agent of this disease. Certain observers, on the other hand, oppose this belief and have considered it more likely that streptococcus plays in scarlatina the rôle of a secondary invader. The objections of this latter group to the etiological significance of streptococcus are based upon certain important considerations. As is well known, streptococcus is an organism of very widespread distribution and gives rise to a variety of pathological lesions, such as abscess formation, cellulitis, septicæmia and numerous other conditions. Frequently the same individual may have throughout life repeated streptococcus infections, one attack not seeming to confer immunity against subsequent invasion of the tissues by the same organism. The latter condition of affairs is especially true of erysipelas, one of the most characteristic of the streptococcus diseases. On the other hand, scarlet fever, in sharp contrast to other streptococcus infections, is a fairly definite clinical entity and one attack appears to give rise to an immunity of life-long duration. This peculiarity of scarlet fever might have been explained had it been possible to prove that the streptococcus associated with scarlet fever differed specifically from the hæmolytic streptococci causing the various septic processes. However, early cultural and biochemical studies have failed to demonstrate any significant differential characteristics by means of which Streptococcus scarlatinæ could be separated biologically from similar streptococci found in other diseases. When grown in fluid or in solid media, hæmolytic streptococci resemble one another very closely, whatever be their source. It is true that certain constant differences can be brought out by means of fermentation of various carbohydrates, but such variations as exist apparently do not bear any specific relationship to a single disease process, and have been of but little aid in determining the etiological significance of streptococcus in scarlet fever. In addition to this objection, Jochmann [16] has emphasized especially his failure to find streptococcus in either blood or tissue of individuals dying in a few days from malignant forms of the disease. Since, therefore, types of streptococci indistinguishable from

those seen in scarlatina are found in a great variety of disease conditions, and since the quality of the immunity in this disease differs widely in its duration from that observed in other streptococcus infections, and finally because of Jochmann's contention that streptococcus is not present in certain malignant types of scarlet fever, the conclusion has been drawn that streptococcus cannot be the cause of the disease.

An effort to meet these objections has been made by the group of investigators who believe that streptococcus is the etiological agent of scarlet fever. The observation by Baginsky and Sommerfeld of the constant presence of S. hæmolyticus in the throats of all cases of scarlatina, an observation later confirmed by others, has done much to offset the inferences drawn from Jochmann's failure to find it in a few instances of fulminant types, especially since we now know that the organism in the latter cases may have been localized in some inaccessible area. Attempts were made in addition to explain the immunity in scarlet fever and to establish the type specificity of the scarlatinal streptococcus. Moser [17] and Moser and Pirquet [18] have claimed that scarlatinal convalescent serum agglutinates to a higher titer Streptococcus scarlatinæ than does control serum from other diseases. Furthermore, they have prepared polyvalent serum from horses, using the streptococcus of scarlet fever as antigen and have studied the capacity of such sera to agglutinate specifically various strains of scarlatinal streptococci. The latter strains were agglutinated in dilutions of 1 : 1000 or over, whereas hæmolytic streptococci from other sources were not specifically agglutinated. As a consequence of these observations Moser and Pirquet believed that the streptococcus of scarlet fever differs specifically from apparently similar strains isolated from instances of erysipelas, phlegmon and puerperal sepsis. Meyer [19] and Rossiwall and Schick [20] have confirmed the results of Moser and Pirquet. Unfortunately, however, certain later studies by Hasenknopf and Salge,[21] Aronson,[22] and Neufeld [23] failed to support the earlier ones and grave doubt was thrown upon the specificity of Streptococcus scarlatinæ.

Other interesting facts which indicate the specific relation-

ship of streptococcus to scarlet fever have come from the studies of Gabritchewsky[24] on the specific prophylaxis of scarlet fever by means of a vaccine prepared from S. scarlatinæ, and of Moser[25] on the therapeusis of the disease by means of a specific antistreptococcus serum. Gabritchewsky and his co-workers immunized a large number of individuals against scarlet fever with a vaccine prepared from hæmolytic streptococci isolated from scarlatina. During the process of immunization certain phenomena occurred which were highly suggestive of the clinical manifestations of scarlet fever. In the majority of instances an area of erythema and swelling averaging 15 cm. in diameter developed at the site of the vaccine injection appearing in from eight to twenty-four hours and lasting about forty-eight hours. In general, the erythema was diminished or absent following a second injection some ten days later. In about 15 per cent. of the individuals inoculated a general reaction was observed. This general reaction consisted in fever of 1° C. or so, leucocytosis and an erythematous rash, having the characteristic distribution of the exanthem in scarlet fever. Some of those inoculated showed the typical angina and strawberry tongue peculiar to the disease and in a few instances signs of renal irritation were observed. In general individuals who were recovering from the disease or who had had it some years before failed to show either a local or general reaction. Administration of Moser's antiscarlatinal serum before the inoculation was shown to prevent the development of both a local and a general reaction. Prophylactic immunization of this type seemed to diminish the incidence of scarlet fever among the inoculated. As a result of these observations Gabritchewsky and his assistants were strongly of the opinion that streptococcus is the causative agent of scarlet fever.

The therapeutic results obtained by the use of Moser's serum lent further support to this view. Moser immunized horses to hæmolytic streptococci obtained from the blood of patients suffering from scarlatina. The serum thus prepared was used therapeutically and is said to have had marked beneficial effects causing a drop in the temperature and pulse, a diminution of the toxæmia, early disappearance of the rash and a marked short-

ening of the duration of the disease. Escherich, who observed the work closely, was much impressed by the therapeutic value of the serum and likened its action to that of diphtheria antitoxin. Later antistreptococcic sera prepared by other investigators, however, failed to display the therapeutic efficiency of Moser's serum and created doubt in the minds of many concerning the usefulness of such sera.

Much other evidence both for and against the etiological relationship of streptococcus to scarlet fever was presented at this time and as one weighs its importance in retrospect, the positive seems of more significance than the negative. The outstanding objection, however, to the acceptance of streptococcus as the cause of scarlet fever remained the impossibility of differentiating satisfactorily this organism from hæmolytic streptococci associated with the great variety of septic conditions. As a result, other etiologic agents were searched for. Moser's serum dropped into disuse and streptococcus vaccine was no longer used in the prophylaxis of scarlet fever. Scientific opinion gradually came to hold that streptococcus bore an important but secondary relationship to scarlet fever, and that the true cause must be sought among the unknown viruses.

For many years confusion has existed and opinion has varied concerning the existence of biologically varying types of streptococcus. Two diverging points of view developed, one maintaining the unity of the species as a type, and the other holding that it comprised a group of organisms different from one another in their biological characteristics. Schottmüller [26] in 1903 made an important contribution to the discussion in demonstrating between certain streptococci, differences based on their action on blood agar plates, one group hæmolyzing the red blood cells and the other either failing to hæmolyze or forming methemoglobin. This significant differentiation resulted in the establishment of the types now generally recognized as hæmolytic and nonhæmolytic or green pigment producing strains. Further classification was attempted by numerous investigators who used as a basis of differentiation certain biochemical reactions. Holman [27] in 1916, using carbohydrate fermentation as a

test, was able to demonstrate the existence of a number of separate fermentation types. Numerous efforts were also made to establish biological differences, especially among the hæmolytic streptococci, by means of serological reaction methods which had proven singularly successful when employed for studying the various types of pneumococcus and meningococcus. As a result of these studies conflicting beliefs arose, and a definite opinion could not be given as to whether or not separate biological types of S. hæmolyticus exist. As late as 1918 Swift and Kinsella,[28] using the complement fixation reaction as a test, made a series of observations of twenty-eight strains of hæmolytic streptococcus from various sources. They found that they were unable to determine significant serological differences between the strains studied and are of the opinion that a striking homogeneity exists. Efforts to correlate such different types of hæmolytic streptococcus as had been determined with specific pathological lesions were also of indeterminable significance, varying types being found in association with the same disease.

In 1918 Dochez, Avery, and Lancefield [29] undertook a biological study of a great number of strains of S. hæmolyticus, obtained from a variety of pathological conditions among the changing population of a large military establishment. The purpose of this investigation was to determine if there exist among the hæmolytic streptococci diverse biological types, as is the case in the instances of pneumococcus and meningococcus. The specific test reactions were those of agglutination and protection. Spontaneous non-specific flocculation, the most confusing factor in previous studies of specific agglutination of streptococcus, was avoided by the employment of special methods. The outcome of these studies was to prove that there are separate biological types among hæmolytic streptococci, just as there are among other apparently closely related groups of microörganisms. More than 68 per cent. of the strains investigated comprised six easily distinguishable serological types.

This study was part of a general investigation of the biology of streptococcus, and, as a result of the facts developed, Bliss and Dochez [30] undertook a reinvestigation of the much debated ques-

tion of the unity of type of the S. hæmolyticus so constantly associated with scarlet fever. An effort was made to answer Jochmann's main objection to the etiological relationship of S. hæmolyticus to scarlet fever, namely, that the organism is not present in every instance of the disease, and that it cannot be satisfactorily differentiated from hæmolytic streptococci associated with the common septic conditions. Bliss [31] found when cultures are made from the throat early in the course of scarlet fever that hæmolytic streptococci are present in predominating numbers in 100 per cent. of individuals examined, thus confirming the earlier work of Baginsky and Sommerfeld. Immune sera were then prepared by the inoculation of rabbits with scarlet fever streptococci, and the capacity of these sera to agglutinate specifically a large number of freshly isolated scarlet fever strains was tested. Ten such sera were prepared from different strains of scarlet fever streptococci and each serum was found to agglutinate more than 80 per cent. of the strains isolated from scarlatinal throats. Agglutinating sera prepared from strains of hæmolytic streptococci derived from pathological sources other than scarlet fever in general, failed to agglutinate specifically the scarlatinal strains. Furthermore, strains of hæmolytic streptococci obtained from such conditions as tonsillitis, erysipelas, bronchopneumonia, and other septic diseases, as well as the various type streptococci, determined by Dochez, Avery and Lancefield were not agglutinated by the scarlatinal antistreptococcic sera. The evidence in favor of the specificity of the agglutination reaction of scarlatinal streptococci was reinforced by results obtained from agglutinin absorption experiments. Scarlatinal streptococcic sera also afforded some protection of experimental animals against virulent scarlet fever streptococci, but had no protective power against hæmolytic streptococci from other sources. This work indicates that the majority of hæmolytic streptococci found in association with scarlatina belong to a specific biological group and can, by appropriate methods, be distinguished from hæmolytic streptococci derived from other pathological conditions. These observations, I believe, confirm in a satisfactory manner the early studies of Moser and von Pir-

quet on the same subject. Contemporaneously with Bliss, Tunnicliff [32] investigated, by means of the opsonic and agglutination reaction, a series of hæmolytic streptococci isolated from patients during the early stages of scarlet fever. She concludes that the serum of sheep immunized with hæmolytic streptococci from the throat in the acute stage of scarlet fever contains opsonins and agglutinins for the hæmolytic streptococci that prevail in the throat and complicating lesions early in this disease, but not for hæmolytic streptococci from other sources, such as erysipelas, mastoiditis, measles, influenza, diphtheria and the normal throat. The results of her absorption experiments also indicate that the hæmolytic streptococcus from scarlet fever forms a distinct group, scarlatinal streptococci removing the opsonins and agglutinins for these cocci while absorption with a hæmolytic streptococcus from erysipelas has no such effect. These results also suggest that the hæmolytic streptococci from scarlet fever form a distinct serologic group. Somewhat later Gordon [33] found that eighteen strains of hæmolytic streptococcus isolated from scarlatina were identical in their agglutinative reactions. None of these strains absorbed the agglutinins from immune sera prepared from certain other types of hæmolytic streptococcus, designated by him as Types I and II. On the basis of this evidence, Gordon concludes that the streptococci from the throat secretions in scarlet fever constitute a group immunologically distinct from other varieties of streptococcus pyogenes. Eagles [34] in a recent study compared the serological reactions of hæmolytic streptococci from scarlet fever, puerperal sepsis, erysipelas and miscellaneous sources. He confirms the immunological specificity of the scarlatinal group and the clearness with which it can be separated from other types of streptococcus. He furthermore compared in an interesting manner a number of individual strains obtained at three to four day intervals from the same patient and demonstrated a gradual but progressive loss of specific agglutinability, a phenomenon which we have observed, and of which I shall say more later. Williams [35] has also studied the serological reactions of the scarlatinal streptococci and finds only 35 per cent. to belong to a single type, and is of the opinion that a greater

variability exists than is suggested by the work of the previous observers. Dick and Dick [36] have shown two strains of scarlet fever streptococci, one a mannite fermenter, and the other a non-mannite fermenter, to be serologically distinct, and believe that the agglutination reaction is of but little importance in determining the character of the scarlatinal streptococci.

It would seem, therefore, that the old question stressed by Jochmann, concerning the specificity of the streptococcus of scarlet fever still remains in dispute. The preponderance of evidence, however, strongly favors the belief that these cocci comprise a separate biological group and that the best method for determining this specificity of type is by agglutination. In order that satisfactory results may be obtained from this reaction certain rigid conditions must be complied with; spontaneous auto-agglutination must be prevented, and the streptococci in question must be studied fresh from their human environment. This latter requirement is of great significance. Recent studies by Avery and Heidelberger [37] have shown that the type specificity of pneumococcus is dependent upon the chemical constitution of the capsular substance. The production of this substance is a variable function of the organism; it is greatest in its strictly parasitic phase and is reduced by all factors which reduce virulence and lessen pathogenicity. That a similar loss of a specific function by scarlatinal streptococci takes place when they are removed from their parasitic environment is extremely likely. Bliss and Stevens and Dochez [38] have emphasized the rapidity with which specific agglutinating qualities are lost upon continued growth of these streptococci in artificial medium and Eagles suggests that the same change may take place under the influence of the immune bodies formed by a scarlatinal subject during convalescence. The suppression of specificity of serological reaction under the influence of immune bodies is, of course, a well recognized and established phenomenon among the pneumococci. The results obtained, therefore, indicate that if a large number of strains of scarlatinal streptococci are studied under appropriate conditions and within a short period of time from

their isolation during the acute stage of scarlet fever a high degree of serological specificity can be demonstrated.

Streptococcus scarlatinæ is found not only in the throats and organs of individuals suffering from anginal types of scarlet fever but has also been obtained from atypical forms of the disease, healthy carriers and contaminated food products. Serologically specific streptococci have been isolated from the local lesions in scarlet fever arising from the infection of wounds and burns, from the throat in scarlet fever without a rash, and from the lochial discharge in instances of puerperal scarlet fever. Bliss succeeded in tracing a small outbreak of scarlatina in an isolated children's institution to a recently admitted healthy carrier of Streptococcus scarlatinæ. Stevens and myself identified by means of agglutination and absorption reactions as scarlatinal streptococci organisms isolated both from the contaminated milk which had given rise to a milk-borne epidemic of scarlet fever, and from the throats of patients who contracted the disease from this milk. As a result of these studies the importance of Jochmann's objections to Streptococcus scarlatinæ as the etiological agent of scarlet fever was much lessened and students again began to take an active interest in this organism as the probable cause of the disease.

From the very beginning of the study of scarlet fever efforts have been made to produce the disease experimentally in animals and in man by inoculation with scarlatinal material. Most of these attempts have had in view the demonstration of an unknown virus of the filter passing type. Streptococcus scarlatinæ, in spite of the presumptive evidence in its favor and of the fact that some of the most typical examples of scarlet fever in animals have been associated with its presence has been but little tested for its capacity to produce the disease experimentally. Class [39] in 1899 reported the experimental production of this disease in swine by an organism designated by him as Micrococcus scarlatinæ. This was a gram negative coccus isolated from three hundred cases of scarlet fever and was, in all probability, a streptococcus. Krumwiede, Nicoll and Pratt [40] in 1914 observed an accidental infection of a laboratory worker, who sucked into her mouth a

mixture of living streptococci containing Streptococcus scarlatinæ. Three days later this individual developed a sore throat and subsequently experienced a typical attack of scarlet fever with all the usual phenomena. Because of the interest aroused by this observation, efforts were made to infect monkeys with the same streptococcus, but no instance of the disease was successfully produced.

In 1921 Dick and Dick [41] made a series of human inoculations with certain organisms obtained from the throats of individuals suffering from scarlet fever. Among the organisms utilized for this purpose was Streptococcus scarlatinæ. Though some of the volunteers experienced sore throats as a result of the treatment, no true instance of experimental scarlet fever resulted. In 1923 the same workers [42] repeated their efforts to produce scarlet fever in human volunteers. In the second series of observations a hæmolytic streptococcus obtained from the infected finger of a nurse suffering from wound scarlet fever was used for purposes of inoculation. Five volunteers were inoculated by swabbing the tonsils and pharynx with four-day-old cultures of the streptococcus in question. Three of these individuals remained without evidence of infection and one suffered from sore throat and fever without a rash. The fifth volunteer, however, who had been inoculated with the streptococcus after three weeks' growth in artificial medium experienced a typical but mild attack of scarlet fever, beginning forty-four hours after inoculation, and characterized by sore throat, general malaise, nausea, fever, leucocytosis, a typical rash and albuminuria. Desquamation began on the hands and feet on the tenth day, and was complete by the end of the fourth week. Five volunteers inoculated with filtrates of the above-mentioned organism remained well and showed neither sore throat nor rash. Subsequent inoculation of four of these volunteers with living unfiltered cultures of the original streptococcus resulted in the experimental production of another instance of scarlet fever. These observations were confirmed later by the same investigators [43] by the experimental production of another instance of scarlet fever in an individual proven susceptible by the use of a skin test devised by them.

In 1920 Dochez and Bliss, while studying the biological reactions of Streptococcus scarlatinæ, observed in a dog infected subcutaneously with living organisms, the development of an intense general erythema followed later by desquamation. Attempts to reproduce this phenomenon in dogs resulted in failure. Stevens and Dochez later tried other animals, including monkeys, without success. Failure in these instances seemed to be due to our inability to induce a local infection because of the low virulence of the organism for the animals employed. Finally Dochez and Sherman [44] were successful in producing in guinea-pigs and young swine a series of manifestations comprising some of the principal phenomena of scarlet fever. Successful local infection was achieved by injecting melted agar subcutaneously and infiltrating the mass with living culture of Streptococcus scarlatinæ. Since it had become increasingly evident that scarlatina has a certain resemblance to diphtheria, in that there is a local infection in the throat from which the specific toxic substance is distributed, we hoped that a similar absorption of toxic material would take place from the local area of infected agar. This proved to be the case and guinea-pigs and swine treated in the manner described developed an erythematous rash, fever, leucocytosis and progressive loss of weight. From eight to twelve days following infection the swine had general scaly desquamation and the guinea-pigs slight general desquamation and complete separation of the skin over the pads of the feet. This phenomenon could not be induced when hæmolytic streptococci from sources other than scarlet fever were utilized. Some of the guinea-pigs died acutely from the toxic substances absorbed from the locally infected area, and after death streptococci could not be demonstrated by culture either in the blood or serous cavities.

The production of experimental scarlet fever in human beings and in animals by inoculation with Streptococcus scarlatinæ had by this time made it increasingly likely that this organism is the causative agent of the disease. The evidence in favor of the absorption from the area of local infection of a toxic substance

which might be responsible for the clinical picture, had again brought into the foreground the analogy with diphtheria.

Investigators of scarlet fever have for many years been impressed with the similarity of this disease to diphtheria. Berge,[45] as early as 1895, suggested that scarlatina is due to a local infection in the throat with streptococcus and that the general symptoms of the disease are due, as in diphtheria, to the absorption into the general circulation of soluble toxins formed by the infecting microörganism at the site of the local disease. Gabritchewsky and his co-workers, in their studies of scarlatiniform manifestations which followed immunization of human beings against scarlet fever by means of vaccines of killed cultures of streptococcus scarlatinæ, attributed these reactions to the presence of a toxin in the vaccines. They drew attention to the absence of a vaccine erythema in individuals who gave a history of having had scarlet fever, and its failure to develop in patients during the period of convalescence from this disease.

Much evidence in favor of the existence of a soluble circulating poison in scarlet fever has also come from the study of the so-called Schultz-Charlton extinction phenomenon. In 1918 Schultz and Charlton[46] discovered that if one injects into the skin of a scarlet-fever patient with a bright red rash 1 cc. of serum from a normal person, or from a patient convalescent from scarlet fever, there appears after a time at the site of the injection a characteristic change. This change begins after about six hours and consists in a complete blanching of the rash over an area of from one-half inch to a few inches in diameter. In the affected area the swollen follicles, which are a feature of many rashes, disappear. Looked at from a distance, the margin of the defect in the rash is generally sharply defined. The color of the blanched area is that of normal skin and the duration of the typical phenomenon coincides on the whole with that of the rash itself. On the other hand, serum taken from scarlet-fever patients during the acute stage of the illness invariably gave negative results. Subsequent investigators abundantly corroborated the accuracy of the observation of Schultz and Charlton. As a result of these later studies it was established that the serum

of about sixty per cent. of normal adults possesses the capacity to blanch the rash in an active case of scarlet fever; that convalescent scarlatinal serum gives a positive rash extinction test in from 80 to 100 per cent. of instances; and that the serum during the active stages of scarlet fever never manifests blanching power. The Schultz-Charlton reaction was first used as a diagnostic test of scarlet fever, and the capacity to extinguish the rash in scarlet fever was believed to be due to a normal property of human serum, which is temporarily lost during the acute stage of scarlet fever and regained during convalescence.

In 1923 Mair[47] published a study of the Schultz-Charlton reaction in which he confirmed in general the observations of previous workers but gave the phenomenon a much more satisfactory explanation. He had an opportunity of studying the blanching power of the serum of a child both before and after an attack of scarlet fever and showed that the serum before the attack gave a negative Schultz-Charlton test, but during convalescence acquired the capacity to extinguish an active rash. This disproved the previous belief that a positive reaction was due to some property of normal human serum which is lost during the acute stages of scarlet fever. He also showed that the sera of young children who had not had scarlet fever give a negative reaction in a much greater proportion of instances than do adult sera and that the reactivity of the sera of new-born infants corresponds with that of the mothers.

Mair had been interested for some years in the resemblance of scarlet fever to diphtheria. As a result of his later work, he came to believe that the rash and other changes in the skin in scarlet fever are due to a scarlatinal toxin which has entered into combination with the tissue cells. Among the affected cells are those contractile elements which have been shown to exist even in capillary blood-vessels, and to the function of which the normal tone of the capillaries is due. The toxin interferes with the function of these cells and a loss of tone of the capillaries results in the erythema and exudative phenomena with which we are familiar in the scarlatinal rash. He supposes that the serum giving a positive Schultz-Charlton reaction contains an antitoxin

which is able to dislodge and neutralize the toxin fixed in the cells, and thus restores their normal function over the area injected. He adds that the true causal organism when discovered should be capable of producing a toxin, and that the immunization of animals to this poison should give rise to an antitoxin capable of producing a positive Schultz-Charlton reaction in man.

We also had been pondering over the analogy between scarlet fever and diphtheria and, at the time of the publicatoin of Mair's observations, had already produced in horses by immunization to Streptococcus scarlatinæ an antitoxic serum of the type postulated by him. Struck by the fact that occasionally in guinea-pigs inoculated for the production of experimental scarlet fever sufficient poison was absorbed from the local lesion to kill the animals acutely, we determined to make use of the method for the production of an antitoxic serum in horses. Masses of melted nutrient agar were injected beneath the skin and then infiltrated with increasing doses of Streptococcus scarlatinæ. The animals experienced a general reaction, and some of them, curiously enough, showed loss of hair and extensive general desquamation. After nine months' immunization the first animal was bled and his serum tested by Blake, Trask and Lynch [48] for its correspondence with human convalescent scarlatinal serum. When injected intracutaneously in a patient with a bright rash in the acute stage of scarlet fever this serum caused a complete extinction of the rash over an area five to ten centimetres in diameter. The blanching appeared in from six to twelve hours following injection of the serum and persisted throughout the course of the disease. As a rule, the characteristic pigmentation and desquamation were absent during convalescence over the blanched area. Antisera prepared from other hæmolytic streptococci and from Streptococcus scarlatinæ injected intravenously into animals, failed to induce blanching of the rash. Furthermore, scarlatiniform rashes in such conditions as erysipelas, measles, and other exanthematic diseases were not influenced by the intracutaneous injection of the scarlatinal antitoxin. Injection of a sufficient quantity of the serum intramuscularly in a patient in the exan-

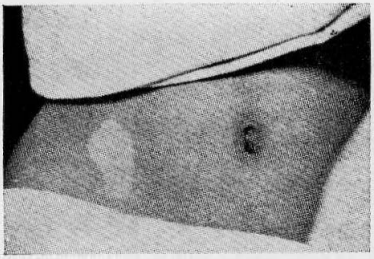

FIG. 1.—Blanching of skin in human scarlet fever due to intracutaneous injection of scarlatinal strep. antitox. (Blake, Trask & Lynch.)

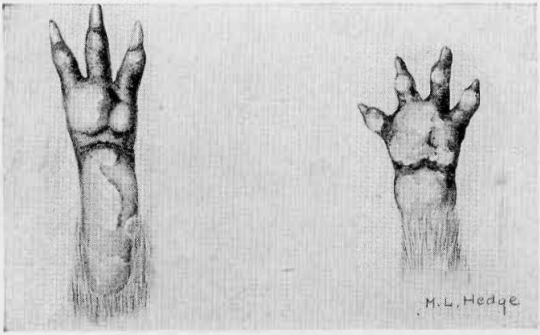

FIG. 2.—Desquamation following experimental scarlet fever in guinea-pigs.

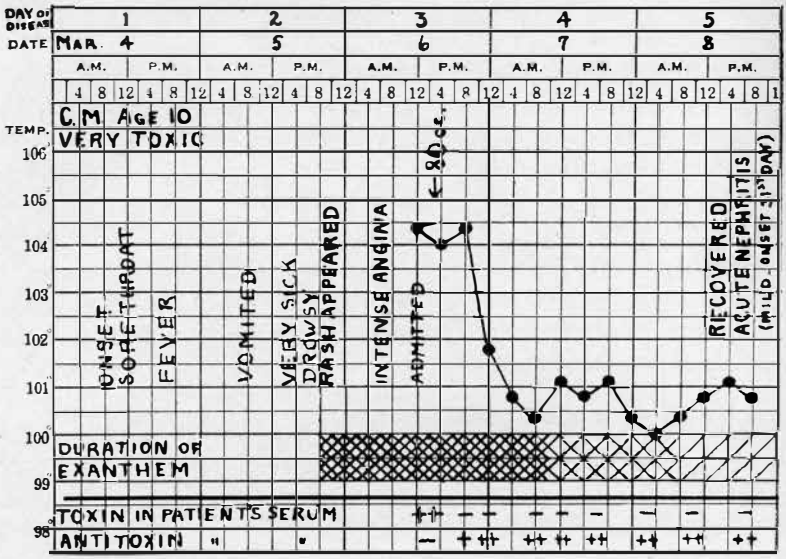

FIG. 3.—Analysis of effect of treatment of scarlet fever with scarlatinal streptococcus antitoxin. (Blake & Trask.)

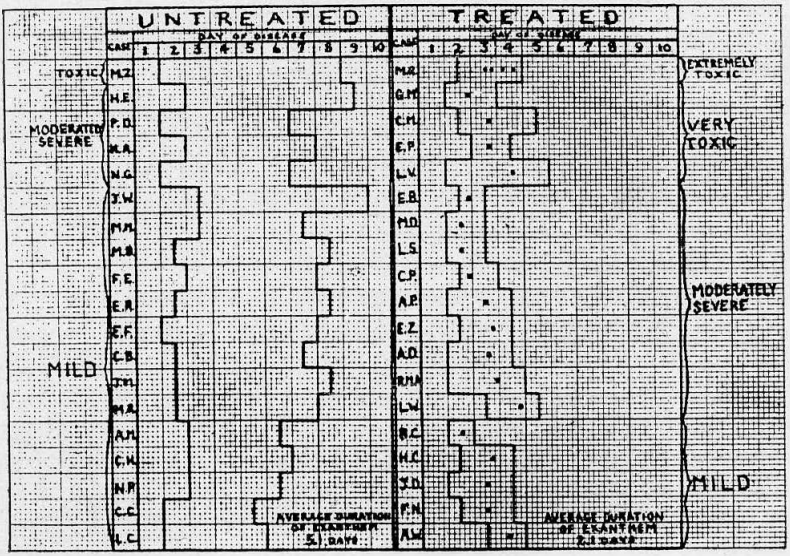

FIG. 4.—Comparative duration of rash in untreated patients and patients treated with scarlatinal streptococcus antitoxin. (Blake & Trask.)

thematous stage of scarlet fever causes a complete fading of the rash over the whole body in from twelve to twenty-four hours.

Blake and Trask [49] have demonstrated that there is present in the circulating blood and in the urine during the acute stage of scarlet fever a toxic substance which causes an erythematous reaction when injected intracutaneously in individuals whose blood serum gives a negative rash extinction test. This substance appears to be identical with the culture toxin of the Dicks and circulates in the blood for several days. When patients with scarlet fever having easily demonstrable amounts of this poison in the blood are injected with scarlatinal antitoxin, the circulating toxin is rapidly neutralized, a single dose of forty cubic centimetres causing its complete disappearance throughout the remaining course of the disease. The antitoxin quickly predominates in the blood and the treated patients' serum acquires the capacity to induce a positive Schultz-Charlton extinction test, a property that does not develop in untreated patients until late convalescence. The other toxic manifestations of the diseases are likewise favorably influenced. An immune horse serum, therefore, prepared in the manner described, seems to contain a potent antitoxin and behaves in every way in a manner similar to human convalescent scarlet fever serum.

The further studies of Dick and Dick [50] demonstrating the presence of a toxic substance in filtrates from blood broth cultures of Streptococcus scarlatinæ have brought to light a number of new and important facts which develop still further the analogy between scarlet fever and diphtheria. The toxic filtrate was obtained by these authors from a strain of streptococcus with which they had produced experimental scarlet fever in man. When individuals who give a negative history for scarlet fever are injected intracutaneously with small amounts of this toxin, within about six hours there appears at the site of inoculation a small circular area of erythema, which increases in size and intensity of color for from eighteen to thirty-six hours. Frequently the local reaction is accompanied by swelling of the skin. When a series of normal persons who have not had scarlet fever are injected with this substance, 41.6 per cent. of these

show a positive erythema reaction in the skin, a manifestation resembling the Schick test for susceptibility to diphtheria. The remainder who give a negative reaction are considered to be immune, because of the probable presence of circulating antitoxin in the blood, just as in the case of diphtheria. In addition, patients who are recovering from scarlet fever when tested intracutaneously with this substance, give but a very faintly positive or uniformly negative skin reaction. A similar condition of affairs is found to exist among those who have had scarlet fever at some earlier period of life. If individuals who have been proven susceptible to scarlet fever by means of the Dick test, are injected subcutaneously with larger amounts of the toxin, they exhibit certain of the toxic manifestations of the disease, such as nausea and vomiting, fever and an erythematous rash. When toxic filtrate is mixed *in vitro* with a small amount of convalescent scarlet fever serum, its capacity to produce a positive skin reaction is completely neutralized. Neutralization of the reaction was also obtained *in vivo* by the injection into susceptible human beings of larger quantities of convalescent serum. More recent studies of the Dicks [51] have shown that individuals who react positively in the skin can be immunized by repeated doses of the toxin, so that within a relatively short period of time the skin reaction becomes negative, and there is some evidence to support the belief that such individuals may be immune to the disease scarlet fever.

Zingher,[52] in an extensive study, has confirmed the observations of the Dicks and extended them somewhat. He has shown that the Dick reaction is positive in the early stages of scarlet fever in most instances, and that it becomes increasingly negative as the disease progresses through convalescence. He has, furthermore, drawn a very close analogy between the data obtained from the Schick test in diphtheria and those obtained from the Dick test in scarlet fever. In general, susceptibility to the latter reaction is greater in childhood and diminishes in adult life. There is also an inherited resistance to the toxin in infants whose mothers exhibit a negative reaction.

These studies, therefore, indicate that there is present in

sterile filtrates from cultures of Streptococcus scarlatinæ a toxic substance which bears a specific relationship to scarlet fever. By means of this substance it is possible to detect susceptibility in persons who have not suffered from scarlet fever, and furthermore to demonstrate the development of immunity in patients who are recovering from an attack of the disease. This work brings further strong support to the belief that Streptococcus scarlatinæ is the etiological agent of scarlet fever.

In 1921 Di Cristina,[53] in Italy, obtained from the blood of patients with scarlet fever an anærobic Gram-positive diplococcus. Other Italian investigators subsequently isolated a similar organism from the nasopharynx, bone marrow, spleen and desquamating skin of children with scarlet fever. This organism, on further study, was found to show specific serological reactions with the serum of recovered cases of scarlatina. Inoculation of children with living cultures of the organism is said to have produced an attenuated form of scarlet fever. Furthermore, prophylactic inoculation with killed cultures prevented the development of scarlet fever among a number of children exposed to the disease. Unfortunately, we are not in a position as yet to determine with any assurance the significance of this organism in scarlet fever, since an opportunity to study it bacteriologically has not been afforded.

Have we now reached the end of man's long struggle to find the cause of this interesting and at times formidable and dangerous disease? Personally, I think we have. Belief that scarlet fever may be caused by a protozoan parasite, or by one of the mysterious ultramicroscopic viruses, must, I think, be discarded in view of the fact that the evidence brought forward in support of the causative relationship of such types of microörganisms to the disease is entirely unconvincing. On the other hand, can we say with certainty that scarlet fever is caused by a type of Streptococcus hæmolyticus? Certainly a chain of evidence in favor of this organism has been patiently and progressively forged which is as strong as that in many diseases whose etiology is now accepted without discussion. The constant association of this organism with the primary and secondary manifestations

of the disease, its specific character, its capacity to produce the experimental disease in man and in animals, the ability of human convalescent scarlet-fever serum to neutralize the toxic effects of this streptococcus, the capacity of an antistreptococcus horse serum antitoxic in nature to counteract the specific toxic manifestations of the disease in man, and finally the isolation from Berkefeld filtrates of this streptococcus of a toxic substance which bears a specific relationship to immunity in scarlet fever, leaves little room to doubt that Streptococcus scarlatinæ is the principal and probably only etiological agent of scarlet fever.

Let us, therefore, be optimistic and assume that a just reward has come to those many soldiers in the army of science, too numerous to be mentioned in so short an exposition, and that another disease has been added to those about which the essential specific facts are known. Let us also hope that the methods of prevention and treatment based on these facts may prove as successful as the promising character of the preliminary work suggests.

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