SCARLET FEVER

ITS HISTORY AND CONTROL

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Scarlet Fever is an acute infectious disease caused by the Streptococcus scarlatinae, and is generally characterized by sudden onset with fever, sore throat and a generalized punctate eruption followed by desquamation. The intensity of the disease and eruption may vary to a marked degree in different individuals.

The study of the history of scarlet fever is beset with two chief difficulties, inasmuch as not only in the remote past but until comparatively recent times it was almost impossible to disentangle the description of scarlet fever from that of other acute exanthemata, especially measles and erysipelas on the one hand and from that of diphtheria on the other.

An attempt has been made by some writers to trace back the history of scarlet fever to classical antiquity, but many of their accounts are far from convincing. Sanne remarks that certain passages in Hippocrates have given rise to the belief that he was familiar with scarlet fever, owing to his speaking of an illness attended with a severe sore throat, though he makes no mention of a rash. There are also objections to the belief of writers, such as Willan, who think they have found allusions to scarlet fever in certain passages in Celsus, Coelius Aurelianus, Aretaeus of Cappadocia and Aetius of Amida. Bateman credits Herodotus, a physician belonging to the pneumatic sect, who flourished at Rome under Trojan about half a century before Galen, with describing "with some precision" the rashes of scarlatina, although his account is far from convincing.

The Arabian physicians have also been credited with allusions to scarlet fever, but it is a useless conjecture to take their writings as a vivid description of the malady, scorlatina.

The first undoubted description of scarlet fever in medical literature is to be found in the works of John Philip Ingrassias (1510-1580), who was first professor at Naples and during his last twenty years lived at Palermo, where he was celebrated as an anatomist and a practitioner. In his book entitled De Tumoribus Praeter Naturam, he speaks of a disease known as "rossalia" or "rosania", which consisted of "numerous spots large and small, fiery and red, of universal distribution, so that the whole body seems on fire." "Some there are", he continues, "who think that measles is the same as rossalia, but we have often seen that the two affections are distinct, trusting in our own eyes and not merely in the description of others."

The next important writer on scarlet fever was Baillou (Ballo-nius), who under the title of "rubiolae" described the principal varieties of the disease, including scorlatina anginosa. A few years later Jean Cottyar of Portiers, a contemporary of Baillou, published in Paris in 1578 his work entitled De febre purpura epidemiale et contagiosa libri duo, which is generally credited with having given the first description of scarlet fever in France. Cottyar describes the initial symptoms as general weariness, headache, redness of the eyes, sore throat and fever which may be mild or violent. Some patients, he says, are comatose throughout the di-

sease, while others are wakeful and restless. Purpura appeared on the second or third day, accompanied by delirium and soreness of the throat. Three years before Cottyar published his work, there occurred an epidemic of the malady in Paris, which was accompanied by a very high mortality; medical art being of no avail.

A much more important position in the history of scarlet fever is occupied by Daniel Sennert (1572-1637), who described an epidemic which occurred at Wittenberg in the beginning of the seventeenth century. He identified it with the rossalia of Ingrassias, and described the eruption in terms similar to those used by the Neapolitan writer, "in statu vero universum corpus rubum et quasi appareat ac si universali erysipelate laboraret. Sennert was the first writer to mention scarlatinal desquamation, early arthritis, post-scarlatinal dropsy and ascites. It is noteworthy that although the occurrence of dropsy was recognized as sequela of the disease before scarlet fever was given its name, it was not until two hundred years later, after the appearance of Bright's work in 1827, that its connection with renal involvement was realized. The epidemic which Sennert witnessed was obviously severe and the results of the disease were often fatal. Convalescence was often protracted. In more than one passage he expresses his doubts as to what name he should give the disease. "I should have regarded it," he says, "as erysipelas, but for the fact that

2. Ibid.
it does not attack adults but only children and some of our women call it 'Rottlauf'. The vulgar look upon it as measles, and say of it, 'Die Masern laufen zusammen'.

Before taking leave of Sennert mention should be made of his son-in-law, Michael Doering, who observed an epidemic in Poland during 1625 and also noted the desquamation, rheumatoid pains and anasarca characteristic of the disease. Contrary to what is stated by Noirot and Sonne he expressly mentions inflammation of the tonsils and surrounding parts among the symptoms of the disease.

In 1665 scarlet fever reappeared in Poland, where it was described by Simon Schultz under the name of "epidemic malignant purpura". In the following years it was observed by Royger in Hungary, Ettmuller and Lange in Leipzig, Schroeck in Augsburg, and Ramazzini in Modena. Royger describes a case of which he was in charge in 1636 in a girl aged 20 and did not hesitate to identify it with the "rossalia" of Ingrassias. The patient not only had a dense rash, but also inflammation of the tonsils. "As the fever declined", he says, "a windy tumor attacked the left hand whereby the fever was dissolved." (Obviously a case of early scarlatinal arthritis).

The term "scarlatina" was supposed to have been first introduced into medical literature by Sydenham about 1675. Hirsch, however, doubts if he was the first to use the term, for in Lancellotti's Monum. stor. Moden. 1,208,382, there is a reference under the year 1527 of persons dying of

1. Ibid
2. Ibid.
"male de scarlatina". Godall in the latest edition of his work on infectious diseases has also drawn attention to the term "scarlett fevour" being used in Pepys' Diary on the date November 10th, 1665, the passage being as follows: "My little girle Susan is fallen sick of the measles, or 1 at least of a scarlett fevour." It is, however, an open question whether scarlet fever was really meant in either of these passages, especially in the last where Pepys' applies the indefinite article to "Scarlett fevour."

Richter has pointed out that Sydenham's chapter on scarlet fever did not appear in the 1666 or 1668 editions of the Medical Observations, which was then entitled Methodus curandi febres propriis observationibus superstructa, but was first published in 1683 at Amsterdam, only six years before Sydenham's death, in the first complete edition of his works; while the Processus integri in morbis fere omnibus curandis, which contains a shorter account of the disease in Chapter VIII, was first published in 1693, or four years after Sydenham's death.

Sydenham's description of scarlet fever in the Medical Observations (Section VI, Chapter 2) runs as follows: "Scarlet fever may appear at any season. Nevertheless it oftenest breaks out toward the end of the summer, when it attacks whole families at once, and more especially the infant part of them. The patient feels riford and shivering, just as they do in other fevers. The symptoms, however, are moderate; afterwards, however, the whole skin becomes covered with small red maculae, thicker than those of measles, as well as broader, redder and less uniform. These last

1. Ibid.
for two or three days and then disappear. The cuticle peels off and
branny scales remain lying on the surface like meal. They appear and dis-
appear two or three times." The disease, in his opinion, was merely
a moderate efflorescence of the blood arising from the heat of the pre-
ceding summer or from some other exciting cause.

As regards treatment, Sydenham expressed himself as chary of
both of blood letting and clysters on the one hand and of the cordials on
the other hand. Complete abstention from animal food and feremnted li-
quors he regarded as sufficient treatment. Although the patient should
be kept indoors, it was not necessary to stay continuously in bed. When
the desquamation was complete the patient should be purged with some mild
laxative suited to his age and strength. "By treatment thus simple and
natural", he continues, "the ailment we can hardly call it more is dispell-
ed without either trouble or danger, whereas if on the other hand we over-
treat the patient by confining him to bed or throwing in cordials or other
superfluous and overlearned medicines, the disease is aggravated and the
sick man dies of his doctor", ("nimia medicij diligentia").

In the concluding paragraph he alludes to the possibility of fits
or coma occurring at the onset of the eruption, for which he recommends the
application of a large blister at the back of the neck and a draught of the
syrup of poppies.

The mild character of the disease as Sydenham knew it is known

927, November, 1928.
2. Ibid.
not only by what he expressly says "hoc morbi nomen, vix enim altius adsurgit", but also by his making no mention of the sore throat and of the complications of rheumatism and dropsy already described by Senner and Doering. It is possible, however, as J. F. Payne suggests that when Sydenham saw a bad case of scarlet fever he failed to recognize it as such. Payne adds that the inadequate description of the disease given by Sydenham largely contributed to the misunderstanding of scarlet fever and sore throats in the next century. On the other hand, inadequate as Sydenham's description was, we must be grateful to him for establishing the autonomy of scarlet fever and giving it a name to distinguish it from the other acute exanthemata, particularly measles.

It is, therefore, a regrettable fact that Sydenham's contemporary and successor Richard Morton maintained that scarlet fever was absolutely the same as measles, and only differentiated from it by the character of the eruption. "Let this fever", he says, "be expunged from the roll of diseases, unless it seem good to give it the name of confluent measles." Unlike Sydenham, he described a malignant as well as a mild form and recorded eleven cases which had occurred in his own practice, in both children and adults, including two of his own daughters, aged seven and eight years.

Like Sennert and Doering and unlike Sydenham, Morton expressly mentions inflammation of the fauces in the acute stage and alludes to dropsy and ascites as sequelae. He also appears to be the first author to

1. Ibid.
note the occurrence of scarlatinal otitis, in a sentence where he speaks of an acrid and corrosive discharge from the nose, ears, and throat. (Exercitatio tertia, Cap. 5).

In spite of Morton's attempt to identify scarlet fever with measles, the distinction established by Sydenham was henceforth accepted by subsequent writers in the seventeenth and eighteenth centuries, such as F. Hoffman, Juncker, Cullen, Frank and Vogel. Juncker, in particular, in his Compendium medicinae theoretico-practicae (1724), adopts Sydenham's view of scarlet fever being an attempt of nature to rid herself of acrid caustic matter, and as a harmless disease if left to itself, but likely to be troublesome if treated by a too hot regimen.

It is true that an attempt was made in the beginning of the nineteenth century by Jahn, Piorry and Lheritier to revive Morton's unitarian doctrine, the last two writers inventing the term "hemo-dermite morbill-euse" to include both scarlet fever and measles. Their views, however, did not meet with any acceptance.

Scarlet fever seems first to have been recognized in Scotland, at the end of the seventeenth century. Sir Robert Sibbald, physician to Charles II, president of the College of Physicians of Edinburgh, and Geographer of Scotland, in his work Scotia Illustrata, published in 1684, speaks of scarlatine as one of the many other diseases which had arisen in that century, and suggests that it was due to the "depravities of the humours which have resulted from a growth of luxury." In the experience

of Sibbald, who describes a case in the daughter of a judge of the High Court, the disease was rare and not often fatal.

According to Lutzeft the epidemic of Copenhagen, described by Ole Borch under the name of "rosalia squamosa" was scarlet fever and was probably the first outbreak of the disease in Denmark. It was not, however, until 1760 that the first Danish monograph on the disease entitled De febre scarlatina, was published by Wernicke.

During the eighteenth century numerous epidemics of scarlet fever occurred throughout Europe and the United States, and were described by various writers, the best known of whom were Huxham, Fothergill and Withering in England, Storch and Zimmerman in Germany, De Hoen in Holland, Plenciz in Austria, Rosen von Rosenstein in Sweden, Tissat in Switzerland, and Benjamin Rush in the United States, but most of these epidemics were mild in nature.

The first epidemic of scarlet fever in the United States was described by William Douglass in 1736. However, from the description of the disease given by Sydenham it was hardly likely that the disease observed by Douglass with its severe and fatal complications and sequelae would be identified with the mild, harmless one of Sydenham. Although Douglass says that some cases were called a "scarlet fever", he describes the disease as a "new one", to which he gives no name. Douglass gives an account of the epidemics, appearing in New England in 1735 and 1736, under

1. Ibid.
title, "The Practical History of a New Epidemical Eruptive Miliary Fever, with an Angina Ulcusculesa, which appeared in Boston, New England, in the years 1735 and 1736". His conception of the disease was more accurate than that of the early English writers, for he recognized the disease as an eruptive fever, often with an associated ulcerative angina. He describes fully the eruption and desquamation, and speaks of the greater susceptibility of children and young persons and the part played by individual susceptibility among these and remarks, "our epidemick is attended with no cough, unless when complicated with a cold or some habitual tussis".

Although scarlet fever was generally regarded in the eighteenth as a distinct disease from measles, there was a tendency to confuse it with angina maligna, which was not finally established as a distinct disease until the next century, when Bretonneau gave it the name of "diphtherite" in 1821. Withering, for example, at first was of the opinion that scarlatina anginosa and angina gangrenosa were distinct diseases, but afterwards became convinced that they constituted but one species of disease; while Willan had no hesitation in ranking the "garrotillo" among the varieties of scarlet fever. Cullen, on the other hand, expressed the opinion that scarlet fever was specifically different from angina maligna.

Among the eighteenth century writers special mention must be made of Rosen von Rosenstein, who in his work on the diseases of children, described the occurrence of scarlet fever at Upsala in 1741 and at Stockholm

in 1761, noting the appearance of secondary adenitis on the eighth or ninth days and of anasarca between the eighteenth and twenty second days. He is also one of the warliest, if not the first, writer to mention the possibility of a non-eruptive scarlet fever. The disease in his experience varied considerably. He stated "The scarlet fever is sometimes and in some persons so favourable and gentle that the patients require only good nursing; whereas, sometimes it is so lethiferous that it will carry off the patients in a day or two." In the like manner, De Haen, after speaking of the light form of scarlet fever seen by Sydenham, describes the malignant outbreaks at the Hague in 1748 and 1749, and alludes to the malignant epidemic which had occurred some years previously in Etruria.

During the last thirty years of the eighteenth century, even when allowance is made for the prevalence of diphtheria, there was a considerable increase in the incidence of scarlet fever, epidemics of which occurred in England, France, Germany, Italy, Holland, Sweden, Denmark and North America. The outbreaks for the most part were mild in character, but an epidemic in central Germany which lasted from 1795 to 1805 was attended by an unusually high mortality, which was attributed to the use of sudorifics and stimulants.

Prior to the nineteenth century scarlet fever was treated with superstition only. There were no methods of control. Homeopathically, red rashes of all kinds, especially scarlet fever and measles, were treated by enveloping the patient in red clothing. As early as the beginning

of the eighteenth century, one of the lecturers at St. Bartholomew's Hospital used to say there was exposed for sale in a shop on Fleet Street red "tongues" or tongue-shaped pieces of red cloth, which were tied around the neck of patients suffering from scarlet fever. In Ireland the red rash was cured by applying to the skin of the patient the blood of a hare by means of a red rag; the rag being afterwards buried. During the seventeenth century spittle was a very popular remedy for "breakings out of the skin, and making the skin clear." This belief persisted even during the nineteenth century in many parts of Europe.

We find the use of drugs mentioned in the treatment and control of scarlet fever in the seventeenth century and eighteenth century, when the administration of sudorifics and stimulants were about the only preventive known to medicine. Although many of the narcotics had been known for hundreds of years, they were associated with superstition and therefore feared. Numbered among this group is belladonna. Plants named Strychninos, having a narcotic effect, however, were employed for all manner of external diseases. Belladonna was used in the same respect, for it was thought that the illness came from troubles of the mind. During the middle ages, the poppy along with belladonna and hyoscyamus were thought to have been created by the Devil for the benefit of the witches. The first mention we find made of these drugs is by Hanemann during the epidemic at Konigslutter in 1790, when belladonna was first used against scarlet fever. In 1812, Schenck administered it during the epidemic of Hilschenbuech among 525 persons, among whom he reported a fatality of only three persons. During the fatal epidemics of 1817-1818 and 1819, Bremdt
employed belladonna at Custrin in Germany. In one epidemic he had no
deaths and in the second he reports that "out of 195 persons 14 were
attacked and 181 preserved". It is stated that Newbigging gave it to
69 children when the disease broke out at John Watson's Hospital at Edin-
burgh during the early part of the nineteenth century. Only three were
attacked although 22 cases had already occurred.

In the commencement of the nineteenth century the tendency of
malignant and extensive epidemics to be followed by periods of lesser pre-
valence and low mortality is well illustrated by the experience of Graves
in Dublin and of Bretonneau in Tours. According to Graves the epidemic
of 1801–1804 was extremely fatal, death sometimes taking place on the
second day, whereas the frequent epidemics which followed during the next
twenty-seven years were always of mild character. Subsequent epidemics
of malignant scarlet fever which broke out in Dublin in 1831 and 1834
caus ed more deaths than cholera had done two years before or typhus did
some years later. Similarly, Bretonneau, who had never seen a death from
scarlet fever in his practice during the period 1799–1822, in less than
two months of the year 1824 experienced an epidemic at Tours attended with
so high a mortality that he came to regard scarlet fever as no less deadly
a disease than plague, typhus or cholera. Bretonneau clearly differentiat-
ed scarlatinal angina from diphtheria by pointing out first that in scar-
let fever the inflammation is widely diffused over the tonsils, palate
and pharynx is not as in diphtheria at first limited to one spot; and
secondly that the scarlatinal inflammation of the pharynx has no tendency

1. Moore, G.: Scarlatina Prevention by Belladonna and Carbolic
to spread into the respiratory passages. Trausseau, who constantly acknowledged his debt to his old master, epigrammatically sums up the last distinction in the sentence, "La scarlatine n'aime pas le larynx."

The chapter on scarlet fever in Trausseau's clinical lectures contains a masterly description of the disease, in which he not only develops the doctrines of Bretonneux, but also draws attention to the characteristic tachycardia, fall of temperature by lysis, frequent occurrence of miliaria, and gives his celebrated account of the "formes frustes", or defaced types of the disease.

In the course of the nineteenth century several parts of the world, which had hitherto escaped, received their first visitation of the disease, such as Madeira in 1806, South America in 1829, Greenland in 1847, Australia and New Zealand in 1848 and California in 1849.

The first step in the control of scarlet fever was made in 1869, when Dr. William Budd of the British Royal Infirmary advocated the following:

"1. The room in which the patient is is detached and dismantled of all needless woolens and draperies.

2. A basin, charged with chloride or carbolate of lime is kept constantly in bed.

3. A large vessel, containing water impregnated with chlorides or with Condyl's fluid always stands in the room for the bed and the body linen.

4. Pocket handkerchiefs are prescribed.

5. Two basins containing water with Condy's fluid always on hand for the nurses use.

6. All glasses, cups and other vessels to be scrupulously cleanse.

7. Discharges from the bowel and kidney are received on their very issue from the body into vessels charged with disinfectants."

At this period many preventative were being tried out, such as rhubarb in doses sufficient to produce one loose evacuation per day, calomel, calomel and antimon, emetics followed by diaphoretics, mineral acids, camphor and capsicum, but the evidence shows that these all proved to be failures.

According to the Registrar-General's report for the ten years ending 1860, the total deaths from all causes in England in males under five years of age was 916,882, females 789,701; those from scarlatina at the same age was 54,665 males and 51,242 in females. According to these figures, there were 59 deaths from scarlatina in males and 64 in females to 1,000 deaths from all causes annually. However, the old confusion between malignant angina and scarlatinal angina prevented the earlier returns from being strictly comparable.

Thus, from the preceding review we may see that the contagious nature of scarlet fever was known at an early date and also that one attack conferred a lasting immunity, but that relapses and secondary attacks may occur. It was learned that the contagiousness of the fever lasts beyond the acute stage and was more nearly coincident with the time required for desquamation. Equally well known was that survival from the acute stage
did not insure against death from complications and sequelae. It was also learned that the disease varied greatly in severity in various epidemics and in different individuals in such epidemics.

Although the causative organism was not definitely found and confirmed until after the World War, we find that investigators had described a streptococcus as the etiological factor for the past fifty years. Klein in 1876 described the occurrence of masses of micrococci on ulcers of the throat in scarlet fever. In 1804 Huebner and Bahrt found in a case of scarlatina complicated by retropharyngeal abscess and suppuration of the finger and knee joints, a streptococcus identical in form to streptococcus pyogenes. Loeffler, in cases of scarlatinal diphtheria, found in the throat and organs streptococci which he cultured and examined. As he was unable to distinguish these streptococci from microorganisms of the same type derived from cases of diphtheria and as he was unable to distinguish them from streptococcus pyogenes or the streptococcus of erysipelas, he concluded that the streptococci which occur in scarlatina, as in diphtheria, are only accidental concomitants.

Crooke, in 1885, demonstrated the presence of streptococci in the organs of persons who had died from scarlet fever. Gordon, in 1909, pointed out that practically all observers agree that the organism most commonly present is the streptococcus, but that it is with respect to its role that opinions so widely differ. He states that the chief streptococcus associated with the disease, is one giving no clot in milk, no neutral red reduction, is positive in saccharose, lactose, salicin, negative in reffinose, mannite and insulin and growing on gelatin at 22 de-
degrees centigrade. Clendening, in 1918, reports on the incidence of re-
infected with the streptococcus hemolyticus in lobar pneumonia, measles,
and scarlet fever as observed in the base hospital at Fort Sam Houston.
Moody and Irons, in 1920, isolated typical hemolytic streptococci from
the feces of 30% of 85 scarlet fever patients. Dochez investigated
agglutination reactions of different strains of streptococcus hemolyticus
from the throat of scarlet fever patients and found that the strains were
closely allied, but could be differentiated. He found a more or less
specific group of streptococci associated with scarlet fever.

He was able to produce symptoms of scarlet fever in guinea pigs
by local subcutaneous injections. He believed at this time that general
symptoms and the rash were toxic in character, but was not able to demon-
strate an in vitro toxin in small amounts that would kill an animal. He
also proved his point by showing that (1) streptococci were present, (2)
they were specific, (3) they produced lesions in guinea pigs, (4) they
were differentiated immunologically from other types of streptococci and
(5) an animal immunized against this organism produces a serum which can
cause a local disappearance of the rash as does the convalescent serum of
a patient who has been ill with scarlet fever.

The etiology of the disease was not definitely established until
George and Gladys Dick concluded from their experiments that all cases of
scarlet fever are caused by the hemolytic streptococcus. They proved
that by experiments on human volunteers that scarlet fever is a local in-

Abstract. 82:2, 1641. 1924.
fection of the throat caused by a particular type of hemolytic strepto-
coccus which is capable of producing a soluble toxin, absorption of
which toxin causes the general manifestations of the disease. In 1923
they successfully inoculated volunteers by swabbing their tonsils and
pharynx with four day old cultures of the hemolytic streptococcus grown
from the pus taken from the finger of a nurse who had contracted mild
scarlet fever. However, in 1924, they found that the S. hemolyticus
associated with scarlet fever do not in all cases present the same cul-
tural characteristics. Thus all of Koch's postulates, including the ex-
perimental production of the disease in man, were fulfilled, and it is
upon this fundamental discovery that the present effective methods of
treatment of scarlet fever are based.

Mairs paper, which preceded that of the Dicks, was one of the
first to suggest toxin as the active principle of scarlet fever. In 1923
he described the results of the Schultz-Charlton experiments performed in
1919, in which the rash of scarlet fever was blanched by the intradermal
injection of 1 cc. of the serum of a convalescent scarlet fever patient or
the serum of a normal individual, the blanching taking place in about six
hours and remaining as long as the rash remained. Schultz and Charlton
assumed that the reaction was due to a normal property in the blood or its
serum, which was temporarily lost during the acute stage of scarlet fever.

Mair hypothesizes that the reaction is a toxin-antitoxin affair,
that is, that the rash is due to toxin circulating in the blood and becom-
ing fixed in the body coverings, and that the injection of convalescent
serum is really the injection of scarlet fever antitoxin which neutraliz-
es the toxin in the cells and therefore causes the blanching.

He proved this point by taking pooled sera of convalescent scarlet fever patients and causing a positive Schultz-Charlton reaction in acute stages of scarlet fever; whereas when the sera of individuals who never had had scarlet fever or who had never been in contact with a case of scarlet fever was used, the reaction was negative. He was also able to test the sera of patients during the early stages of scarlet fever and also thirty eight days later, finding that early in the disease these sera gave a negative reaction, while later they gave positive reactions.

The years of systematic study preceding the actual proof of the etiological agent had led the Dick's to the conception of scarlet fever as a disease whose general manifestations, particularly the rash, are caused by a circulating toxin, while the streptococci which cause the angina remain localized in the throat. Repeated blood cultures made at various stages during the course of the disease except in severely complicated cases near death showed no organisms. On the other hand, by injecting relatively large doses of sterile toxin (the filtrate of 4 day old broth cultures of the streptococcus) they were able to reproduce the typical symptoms of the disease, including the nausea, vomiting, fever and rash in susceptible individuals.

The discovery of the specific toxin of scarlet fever enabled them to develop the following measures to combat the disease:

1. A skin test to determine which individuals are susceptible to scarlet fever and which are immune.

2. A method of actively immunizing susceptible individuals so that they do not contract the disease on exposure.

3. An antitoxin specific for scarlet fever for use after development of the disease and to confer a rapid temporary immunity on susceptible individuals who have been exposed to the disease.


The above four applications of the discovery of the specific toxin, together with the use of the throat and nose cultures on blood agar plates furnished the means of controlling scarlet fever.

Although Dick's theory of the etiology and practice of the control of scarlet fever have found almost universal acceptance, there are still certain individuals who question whether the S. hemolyticus is alone the causative agent of the disease.

Zlatgoroff is one of those who raise this question; his arguments being the most plausible. He says that no specific scarlet fever streptococcus exists. In speaking of the Dick test he says, "The pure toxic character is as yet not generally recognized. At present there is

1. Unpublished paper, "Control of Scarlet Fever, by P. S. Rhoads, read before the Milwaukee County Medical Society, March 8, 1934.
no longer any doubt that the Dick reaction is of relative significance for the demonstration of sensitiveness. The negative Dick reaction does not absolutely indicate the presence of an immunity, and the positive Dick reaction does not positively indicate a great sensitiveness. The transformation of a positive reaction into a negative one must not necessarily be implied as a sign of the development of immunity, since such a transformation may occur not only when the streptococcal derivatives are used, but also by the use of various indifferent substances, such as nutritive media of various types. The original assumption of Dick, according to which the reaction is positive during the first four days of scarlet fever and is negative during convalescence, has not been found to be absolutely correct. The numerous exceptions lead to the assumption that in the Dick reaction we have to deal not only with the elements of toxicity and neutralization, but also with an allergic component. This factor differentiates considerably the Dick from the Schick reaction. According to Cooke, there is no parallelism between the Dick reaction and the antitoxin content of the blood. A negative Dick reaction may be associated with a complete absence of antitoxins in the blood. According to Miller and others, the Dick reaction must not be interpreted as representing the presence or absence of immunity toward scarlet fever, but simply shows a peculiar constitutional condition which favors the onset of scarlet fever. The reaction may be positive in a person who previously suffered from scarlet fever, since the condition of the constitution has not been changed by the disease, in spite of the fact that an immunity towards scarlet fever has been acquired. Of interest are the findings of Leonard and Sander relating to the parallelism between the Dick reaction and the condition of the
nervous system, sympathicotonia and vagatonia, as well as the observations of Block dealing with vagatonia of scarlet fever patients. These observations indicate that the Dick reaction is an indication of the constitution and not a sign of immunity."

In a summary of his experimental work, Zlatgoroff states that, "On the basis of our studies the following views pertaining to the etiology and pathogenesis of scarlet fever may be expressed: In order to give rise to scarlet fever, the hemolytic scarlet fever streptococcus must be activated by a virus. Only such activated streptococci produce a clinical picture of scarlet fever, the origin of which as well as the toxic effect of it is conditioned not only by the streptococci, but also by the effect of the virus. Per se, the virus produces in animals an experimental scarlet fever, a disease sui generis. In man, however, it does not produce the usual symptom complex of scarlet fever, but activates the streptococcus. In some cases this activation is expressed in form of catarrhal changes of the pharynx, and occasionally in form of a skin exanthema, symptoms which point to a change of the streptococci and their pathogenic influences."

The present control of scarlet fever, as previously stated, is practiced according to the theories of Dick, the complete technique of which is well described as follows by Dr. F. S. Rhoads, a co-worker of the Dicks.

The Dick test for susceptibility to scarlet fever is made by injecting exactly 0.1 c.c. of a standardized dilute solution of scarlet fever toxin into the skin of the forearm at the junction of the upper and middle thirds. The technique deserves special mention. It is important that the test be made at this location because the skin of the upper arm is less sensitive to scarlet fever toxin than that of the forearm. No control test is required. Only regular skin test or tuberculin syringes should be used, as accurate work cannot be done with ordinary 1 or 2 c.c. hypodermic syringes. The skin test needles recommended are one-half inch, twenty-six gauge, with soft metal nipples which can be readily molded over the syringe tip and thus prevent leakage, the 'Summit' type manufactured by the D. H. Company. Syringes and needles should be sterilized by boiling in distilled water or dry heat. Alkaline tap water may leave a deposit in the syringes or needles which will destroy the toxin of the skin test solution. Alcohol or other antiseptics should never be used for sterilization, because even minute amounts of such chemicals will destroy the dilute toxin used in the skin tests. Experience has shown that lack of careful attention to these details will lead to inaccurate results.

The tests are observed twenty to twenty-four hours after they are made. Earlier readings will lead to the interpretation of a few negative tests as positive. Readings later than twenty-four hours will cause mistakes in the other direction—that is, a few reactions faintly positive at twenty to twenty-four hours will have faded by twenty-five to twenty-six hours. Any degree of pinkness from the faintest flush to a bright red, one centimeter or over in any diameter, is interpreted as a
positive test, indicating susceptibility to scarlet fever. To avoid
error and to have a basis of comparison when doing retests after comple-
ed immunizing courses the tests should be observed in a bright light and
the reaction recorded in millimeters or fractions of a centimeter.
Putting the skin of the arm on the stretch by squeezing while observing
the reaction may result in error because it obliterates very faintly pink
reactions.

"With attention to all the above details and using accurately
standardized skin test toxin, the Dick test may be depended upon to deter-
mine which persons are susceptible to scarlet fever. More than 40,000
skin tests have been performed by the Scarlet Fever Committee. To our
knowledge only one person found negative to the Dick test has ever con-
tracted scarlet fever, while sixty-eight cases have been observed among
persons reacting positively.

"The number found positive in any group depends on age and pre-
vious exposure to scarlet fever. In adults or children in institutions
where scarlet fever outbreaks have occurred within the past year or two,
not more than ten to fifteen per cent may be found susceptible, while in
young children in communities where sore throats are quickly recognized
and scarlet fever patients promptly and rigidly quarantined seventy to
eighty per cent may react positively. In a series of more than 40,000
persons tested by the Scarlet Fever Committee, including all ages, about
forty per cent were positive and about sixty per cent negative.

Included in this group were 4,000 pupil nurses and internes
with spontaneously negative original tests who were allowed to go on duty in contagious disease wards without immunization. Despite long and continuous exposure to scarlet fever none contracted it. In 1931 I reported the experiences of two and a half years at the Cook County Hospital in attempting to protect a group of 1,280 undergraduate nurses against scarlet fever, 913 of these nurses were Dick tested and 533 (58.4 percent) were found spontaneously immune. None of these originally Dick negative nurses contracted scarlet fever while 15 cases developed among a group of 449 nurses with identical exposures but who had either not been tested at all, or had been found susceptible and incompletely immunized. Since that time one nurse with a spontaneously negative original test has contracted scarlet fever. The cause of error in this test is not known.”

**ACTIVE IMMUNIZATION**

Persons found susceptible by the Dick test may be immunized by injecting gradually increasing doses of scarlet fever toxin. The dosage now recommended is as follows:

A first dose of 500 skin test doses of toxin  
A second dose of 2,000 skin test doses  
A third dose of 8,000 skin test doses  
A fourth dose of 25,000 skin test doses  
A fifth dose of 80,000 skin test doses.

The doses are given subcutaneously below the deltoid at intervals of five or seven days. At times intercurrent illness or other things may necessitate longer intervals between two or more of the doses. If more than three weeks elapse the next scheduled dose may be safely given.
the interval is slightly longer it is advisable to repeat the last dose given, then continue with the course as outlined. When more than two months have elapsed between doses it may be safer to start again with the beginning dose. No animal serum is used in the culture medium in which the toxin is grown, so there is no danger of serum sensitization. Two weeks after the last immunizing dose another Dick test should be done. These reacting positive to the retest should receive a sixth dose the same size as the fifth.

With the dosage as outlined previously approximately 95 per cent are immunized to the point of a negative Dick test. This is about the percentage found immune after known attacks of scarlet fever. Those still reacting positively on the retest almost always have a much modified reaction, including partial but not complete protection.

Reactions following one or more of the immunizing doses occur in many persons. The average local reaction consists of redness and some swelling about the site of injection. No abscesses or sloughs have occurred. General reactions are less common, but do occur in highly susceptible persons. The most severe include malaise, slight rise in temperature, nausea, vomiting and occasionally a mild scarlatinal rash lasting a few hours. These symptoms usually appear within twelve hours and rarely continue beyond thirty-six hours. They are never harmful. Reactions are more apt to follow one or more of the first three injections than the last ones.

If the original Dick test is very bright and covers an area of
more than 30 mm. in diameter, it may be better to give an initial immunizing dose of 250 skin test doses instead of the usual 500 skin test doses. Among the subsequent doses the increase in doses each week may be made more gradually than that just outlined, but the final dose must be 50,000 skin test doses or more if an adequate immunity is to be attained. In those having a sharp general reaction to the immunizing doses, subsequent reactions may be decreased by injecting 0.3 to 0.5 c.c. of epinephrine (1:1000 sol.) with the dose to effect slower absorption of the toxin. Among 190 Cook County Hospital nurses receiving immunizing doses of 1929 and 1930 a total of 45.5 days of duty were lost because of reactions, an average of 0.239 days per nurse immunized.

The duration of the active immunity as well as the degree of immunity depends on the amount of toxin injected. Retests made at intervals of one, two, three, five and six years indicate that more than 90 per cent of those immunized to the point of an entirely negative Dick test retain their immunity. For safety it is advisable to repeat the Dick test at the end of one or two years. If a person is found susceptible on such a retest and again receives the full immunizing course, he usually retains his immunity for at least several years. It is possible to render the majority of susceptible individuals with less than the five doses as above outlined, but the immunity thus produced is not as permanent or as complete as with the full five course dosage. Among more than 6,000 nurses immunized to the point of a negative Dick test at the Cook County Hospital since 1927, none have contracted scarlet fever, while 23 who were either not tested, immunized at all, or incompletely immunized contracted scarlet fever.
USE OF ANTITOXIN

Scarlet fever antitoxin is made from the blood of horses which have received gradually increasing doses of sterile scarlet fever toxin over a period of several months. The serum of this blood is separated, then refined and concentrated and allowed to age. With these procedures which are required of manufacturers licensed by the Scarlet Fever Committee, it has been possible to reduce the number of serum reactions following the administration of scarlet fever antitoxin, to a figure comparable with that following injections of other refined horse sera, such as the antitoxins of diphtheria and tetanus.

Recently L. W. Hunt reviewed serum disease as it occurred at the Durand Hospital for Contagious Diseases since its establishment in 1913. He found that 28.1 per cent of those receiving diphtheria antitoxin experienced serum reactions and 22.7 per cent of those receiving scarlet fever antitoxin had reactions. 81.8 per cent of the patients who received antimenigocococcus serum showed reactions. He found the severity and duration of serum sickness practically identical in the three groups. The impression gained by many physicians early in the use of antitoxin for treatment of scarlet fever that this antitoxin produced more frequent and more severe reactions than other sera, probably arose from the fact that for a short time improperly aged and improperly concentrated sera were used. For the past seven years satisfactorily prepared sera have been available. The reactions occurring after scarlet fever antitoxin injections at the present time are in every way comparable with those occurring after the use of any other properly refined and properly aged serum.
The strength of scarlet fever antitoxin is determined by its ability to neutralize the toxin. One neutralizing unit is that amount which will neutralize one skin test dose of toxin, and hold it in combination for at least forty-eight hours. The therapeutic dose should contain at least 300,000 of these neutralizing units, and the prophylactic dose at least 10,000 units.

The therapeutic dose of antitoxin should be injected deep intramuscularly and soon as the diagnosis of scarlet fever is made. It is advisable to give it even in mild cases because it is known that complications follow in mild cases as well as in the more severe ones. If the attack is severe with the patient very toxic two therapeutic doses should be given at once and more after eighteen to twenty-four hours have elapsed if it is indicated. If the antitoxin is given early in the disease, a prompt falling in the temperature and a fading of the rash may be anticipated. The reports of the Dicks, Hunt, Gordon and others on the therapeutic use of the serum shows that the antitoxin given early shortens the length of the febrile period and reduces the number of complications. The necessity for giving antitoxin early cannot be over-emphasized. If sufficient antitoxin is given within three days of the onset brilliant therapeutic results may be anticipated. There may be an initial rise in temperature, fading of the rash and a clearing up of the subjective features of sore throat and malaise. Antitoxin should be given even later than the third day after the onset, particularly if the rash or other signs of toxemia are still present. However, the benefit derived diminishes directly with the delay in administration.
Convalescent scarlet fever serum is extremely beneficial in therapy also. In addition to furnishing specific antibodies against scarlet fever toxin, it has the advantage of not containing horse serum. However, it is seldom given in adequate dosage. In a recent study, the titer of twelve different lots of pooled scarlet fever convalescent serum was found to average 500 neutralizing units per c.c. This is one-thirtieth of the strength of the weakest scarlet fever antitoxin (14,000 neutralizing units per c.c.) allowed on the market. Hence, to give as many antitoxin units as are contained in a therapeutic dose of antitoxin (300,000) one would have to give 600 c.c. of the average convalescent serum.

PROPHYLACTIC USE OF ANTITOXIN.

Scarlet fever antitoxin may be employed in the prophylactic dosage of 10,000 units to confer a rapid, passive immunity on susceptible persons who have been exposed to the disease. Since the immunity thus produced does not last more than ten days to two weeks, active immunization with the toxin should be started one week after the prophylactic dose has been given.

When possible it is always advisable to do nose and throat cultures on blood agar plates at the time the Dick test is performed on persons exposed to the disease. Even though the individual in question may be susceptible, if his cultures contain no hemolytic streptococci the prophylactic antitoxin may be withheld providing further contact with the scarlet fever patient can be avoided. However, when the "contact" is found to be susceptible and to be harboring hemolytic streptococci in his nose and throat, it is safer to give the prophylactic antitoxin unless the
person can be under strict daily observation. If he can be observed constantly the serum may be withheld until a slight rise in temperature, onset of sore throat or other symptoms of scarlet fever makes its immediate use imperative.

**BLANCHING TEST**

Scarlet fever antitoxin is also used in the diagnosis of doubtful rashes. Two-tenths of a c.c. of scarlet fever antitoxin is injected intradermally in the center of a large area of the doubtful rash, preferably in the abdomen or chest. The test is observed eighteen to twenty-four hours later although it may become positive earlier. A positive reaction consists of a blanching of the rash in a circular zone surrounding the central red spot where the injection was made. The reading should be made in a bright light and is done best by standing at a distance of several feet from the patient. The rashes of German measles and other non-scarlatinal rashes are not affected by the scarlet fever antitoxin.

At this point, a word of caution as to the use of the Dick test in making a diagnosis of scarlet fever may be warranted. Some pediatric textbooks state that these tests made within three days after the onset are almost invariably positive, becoming negative later on in the disease. A recent study by Dr. Benjamin Gasul demonstrated that more than fifty percent of scarlet fever patients when tested on the first day of the attack are found Dick negative when the tests are observed next day. The speed which the Dick test becomes negative after the onset of scarlet fever is so variable that a single Dick test made after the onset is of no value in making a diagnosis. On the other hand, positive cultures for hemoly-
tic streptococci from the nose, throat or surgical lesion constitute strong confirmatory evidence when the clinical features point toward a diagnosis of scarlet fever. Negative cultures, when properly taken early in the course of the disease, are strong evidence against the disease in question being scarlet fever.

**CULTURES IN CONTROLLING SCARLET FEVER**

The use of blood agar plates cultures for the quick control of a scarlet fever epidemic is as the use of Loeffler's medium cultures in diphtheria. With a glass marking pencil the plate should be marked through the diameter and one side marked from throat and the other for nose. The material obtained by rubbing the tonsils and pharynx of the person to be tested with a cotton swab is gently spread over the surface of the "throat" side of the medium, while that obtained by deep insertion of the cotton swab into both nostrils is used to inoculate the "nose" side. The plates are read after twenty-four hours incubation. With a little experience the observer is able to accurately identify hemolytic streptococcus colonies by merely looking at the plate without the aid of a stained specimen. This makes the method rapid and easy. During a scarlet fever epidemic it is best to regard a S. Hemolyticus as scarlatinal streptococci, just as one regards all bacilli as diphtheria bacilli in the presence of a diphtheria epidemic.

**TESTS FOR SPECIFICITY**

The differentiation of scarlet fever streptococci is accomplished by testing the organisms in question for specific toxin production. This
is done by growing the organisms in plain broth to which a small amount of sterile human blood has been added. The broth culture is incubated from two to four days, filtered through a Berkefeld "W" filter to remove the bacteria and the sterile filtrate is tested for the presence of scarlet fever toxin. This procedure requires about the same time and facilities as are needed for testing diphtheria cultures for virulence. It is, therefore, impractical for those who do not have rather extensive laboratory facilities, and it may be left for the health department laboratories.

Fortunately, this test for specificity is not necessary in the majority of instances. It is required only in cases of persistent carriers and under conditions similar to those that necessitate tests for virulence of diphtheria bacilli.

**PREVENTION OF SCARLET FEVER**

Having available all of the means just outlined for combating scarlet fever, namely the skin test for susceptibility, toxin for active immunization, antitoxin, and blood agar plate cultures, practically all outbreaks of scarlet fever can be suppressed rapidly and effectively. The particular method to be employed in homes, schools, camps, institutions, etc. will depend upon the particular conditions confronting each group.

When cases of scarlet fever are not occurring in an institution or a community, all that is necessary is to make skin tests to determine the susceptibility of individuals, then actively immunize them by graduated doses of toxin.

When, however, cases of scarlet fever have occurred in the group
In question the problem becomes more complicated. On the first day Dick tests for susceptibility are performed on every individual of the group concerned, and at the same time cultures from the throat and nose are made on blood agar plates. It is extremely important that everyone be thus tested. For instance in a school the faculty members, janitors, office help, scrub women, etc. must all have throat and nose cultures. Otherwise one carrier of hemolytic streptococci may be missed and the whole effect of the quarantine nullified. If some of the older individuals refuse the skin test that is their own responsibility, but for the welfare of the entire group it is essential that they have cultures. Next day the skin tests are read and the blood agar plates observed. Thus at the end of twenty-four hours it is possible to know for each individual concerned, first, whether or not he is susceptible to scarlet fever, second, whether or not he harbors the hemolytic streptococci in his nose or throat. What is done with each person depends upon these findings.

The school or institution is next divided into two groups depending on the results of the cultures. All those with negative cultures go in one group, all those with positive cultures in the other. They must not under any circumstance be allowed to mingle.

Having made the division into infected and non-infected groups, attention is first turned to those with the positive skin tests, indicating susceptibility, in the infected group. The temperatures of these persons should be taken, their throat examined, and the skin of the chest observed for the appearance of a rash. The finding of a rise in temperature, a suspicious flush of the skin, an inflamed throat or any other symptoms which
arouses suspicion on the part of the examiner should prompt the immediate use of a prophylactic dose of antitoxin. The individual is then put to bed. Daily inspections of this type are continued, and prophylactic antitoxin given when indicated. One week after the quarantine is imposed these susceptible individuals with the positive cultures should be started on active immunization with scarlet fever toxin, whether they have received prophylactic antitoxin or not, but the daily inspection should continue as the active immunization cannot be expected to afford protection until at least three or four doses have been given. Even though one or two doses of toxin have been given, on the appearance of symptoms indicating the onset of scarlet fever these persons should receive antitoxin. The infected individuals who are not susceptible (as indicated by negative skin tests) require no further attention except the throat cultures necessary to release them from quarantine. Under no circumstances should they be permitted to mingle with the "clean" group until their cultures have become negative. In the non-infected or "clean" group the individuals showing negative skin tests may be neglected except to keep them from contact with the infected group so that they will not themselves become carriers. However, those with positive skin tests are started at once on their active immunization with scarlet fever toxin.

The quarantine is maintained until the members of the non-infected susceptible group have received all five of their doses of toxin at five or seven day intervals. Experience has demonstrated the necessity of maintaining the quarantine this long. In most of the institutions where we have worked there have been individuals who have refused active immunization or
have quit after receiving two or three doses. It is a common experience for one or more of such individuals to contact scarlet fever after the quarantine is lifted.

When it is impossible to make cultures on blood agar plates the situation cannot be controlled so quickly. In that case, skin tests should be made at once and the individuals concerned should be divided into two groups depending upon whether they are susceptible or not susceptible. Those with negative skin tests may be disregarded. The group with positive skin tests should be started on active immunization at once, but during this process should be examined daily as outlined before. Therapeutic doses of antitoxin should be given if signs of beginning illness appear. It should always be followed in one week by active immunization.

An example of such a situation, in which culturing was not possible, occurred at Fulton, Illinois, a town of about 1,000 inhabitants. Forty six cases had occurred within three months prior to the time the Scarlet Fever Committee took charge. All the school children from who requests were received from the parents were tested for susceptibility and those found sick positive were immediately started on their toxin injections. In the meantime two school nurses made careful daily inspections of all children in the susceptible group. All children with findings which aroused the suspicions of the nurses were sent home and the children reported to the local health officer. He examined them and gave antitoxin when it was indicated. Two or three cases of scarlet fever developed in the small minority of children whose parents had refused to allow them to
be immunized, but by the time the group of susceptibles had completed their immunization, the epidemic was effectually stopped.

When scarlet fever occurred in a home the same principles of active and preventive treatment apply. The patient receives one or more therapeutic doses of antitoxin. Susceptible "contacts" are started in on their active immunization provided further contact with the scarlet fever patient can be avoided, and frequent observation by the attending physician can be had. On the development of fever, or other signs of early scarlet fever, before immunization is complete, the antitoxin must be administered. If the mother or some other member of the family who is to act as nurse to the scarlet fever patient is found susceptible, she should receive prophylactic antitoxin and then be started on her active immunization one week later, for obviously further contact cannot be avoided. The "contacts" who are not susceptible need not be treated, but should be regarded as potential scarlet fever carriers unless blood agar plate cultures are available to establish the fact that they are not.

In studying results for control of scarlet fever there appears to be some controversy. Much of this controversy seems to be based primarily on the preparation of materials, dosage, methods of administration and precautions to be employed heretofore.

Platou states that, "A study of the reports on 52,200 persons innoculated for the prevention of scarlet fever seems to indicate that: Small doses as first administered were entirely inadequate, a fact attest-
use. Ricinoleated and modified forms of toxin have not as yet proved satisfactory in conferring immunity against the disease. Large doses of pure toxin as recommended by the Scarlet Fever Committee have been effective in the control of institutional and epidemic scarlet fever for as long as four years after their administration.

A summary of the results in 2,430 reported cases of early uncomplicated scarlet fever in which specific streptococcus antitoxin was used shows that temperature recession is usually more prompt in the serum treated cases than in the control cases, the duration of the eruption is shorter in the treated than the untreated case, early symptom improvement is more common in the serum treated cases, desquamation is milder and more localized in those who received serum than in those who did not. In short, Platou agrees with the foregoing unpublished paper by P. S. Rhoads, on the beneficial results of the administration, early in the disease, of scarlet fever antitoxin. Platou takes a more serious regard of the possibility of serum sickness and mentions the possibility of fatal outcome due to the serum reaction. The precautions of importance in the administration of serum are:

1. A careful history concerning
   a. previous serum injections as T.A.T., etc.
   b. asthma
   c. Urticaria.

2. Before any serum is injected a sterile syringe, a small needle and a 1-1000 solution of epinephrine should be at hand. If signs of shock (anaphylactic) appear 0.5 to

1. Platou, E.S.: Minnesota Medicine, 115:697 (October), 1932.
1.0 cc. of the epinephrine should be injected intramuscularly at once.

3. If the patient is found to be sensitive to horse serum he should be desensitized according to the following:

   a. Make a 1-10 dilution of the serum by taking 1/10 cc. of serum and adding 1 cc. of sterile normal saline solution.

   b. Injections may be made as follows every 15 minutes.

      1st injection - 0.25 cc. of 1-10 dilution
      2nd injection - 0.5 cc. of 1-10 dilution.
      3rd injection - 0.1 cc. of undiluted serum
      4th injection - 0.5 cc. of undiluted serum
      5th injection - 1.0 cc. of undiluted serum.

One-half to one hour later the remainder of the amount of the serum may be given, providing no untoward reaction has taken place.

The following table given by G. F. Dick, G. H. Dick and J. E. Gordon show further evidence of the effectiveness of the antitoxin for the treatment of scarlet fever.

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### TABLE I

**Therapeutic Results with Concentrated Scarlet Fever Antitoxin**

*Results in Moderately Severe Cases*

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Deaths</th>
<th>Post-Scarlatinal Nephritis, %</th>
<th>Otitis Media %</th>
<th>Mastoiditis and Otitis</th>
<th>Severe Cervical Adenitis</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Control - 35</td>
<td>0</td>
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<td>4.7%</td>
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<td>0</td>
<td>1.1%</td>
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### TABLE II

*Results in Severe Cases*

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Deaths</th>
<th>Post-Scarlatinal Nephritis, %</th>
<th>Otitis Media %</th>
<th>Mastoiditis and Otitis</th>
<th>Severe Cervical Adenitis</th>
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<tr>
<td>Control Series</td>
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<td>20%</td>
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## TREATMENT OF SCARLET FEVER WITH STREPTOCOCCUS ANTITOXIN

**J.A.M.A., 88:382 (February 5th), 1927.**

### Number of Cases

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<tr>
<th></th>
<th>Deaths</th>
<th>Nephritis</th>
<th>Otitis Media</th>
<th>Mastoiditis</th>
<th>Severe Cervical Adenitis</th>
<th>Arthritis</th>
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<tr>
<td>Control</td>
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<td>8</td>
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### Severe Cases

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<th>Nephritis</th>
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<th>Mastoiditis</th>
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<td>12</td>
<td>2.5</td>
<td>28</td>
<td>8</td>
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<tr>
<td>Antitoxin</td>
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<td>2.2</td>
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### Total Including Mild

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<th>Nephritis</th>
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<th>Mastoiditis</th>
<th>Severe Cervical Adenitis</th>
<th>Arthritis</th>
<th>Total</th>
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<tr>
<td>Control</td>
<td>367</td>
<td>28</td>
<td>4.0</td>
<td>12</td>
<td>2.5</td>
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<td>8</td>
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<tr>
<td>Antitoxin</td>
<td>317</td>
<td>12</td>
<td>2.2</td>
<td>7</td>
<td>0.9</td>
<td>.12</td>
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### Clinical Course

<table>
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<tr>
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<th>Duration of Fever</th>
<th>Days in Hospital after 28th day of Disease</th>
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<td>3.3</td>
<td>6.2</td>
<td>631</td>
</tr>
</tbody>
</table>

### Uncomplicated

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>161</td>
<td>44%</td>
</tr>
<tr>
<td>Antitoxin</td>
<td>210</td>
<td>66%</td>
</tr>
</tbody>
</table>

### One Complication

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>115</td>
<td>31%</td>
</tr>
<tr>
<td>Antitoxin</td>
<td>85</td>
<td>26%</td>
</tr>
</tbody>
</table>

### Multiple Complications

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>91</td>
<td>25%</td>
</tr>
<tr>
<td>Antitoxin</td>
<td>25</td>
<td>8%</td>
</tr>
</tbody>
</table>
### Average Duration in Days of Complication

<table>
<thead>
<tr>
<th>Types of Cases</th>
<th>Cervical</th>
<th>Catarrhal</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenitis</td>
<td>Otitis</td>
<td>Mastoid-</td>
<td>Rhinitis</td>
<td>Rhinitis</td>
</tr>
<tr>
<td></td>
<td>Media</td>
<td>and</td>
<td>and</td>
<td>Albumin-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sinusitis</td>
<td>Sinusitis</td>
<td>Nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medical</td>
<td>Arthritis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Control</td>
<td>146</td>
<td>10.9</td>
<td>17</td>
<td>26.8</td>
<td>24</td>
<td>5.9</td>
<td>3</td>
<td>6.7</td>
<td>9</td>
<td>8.6</td>
</tr>
<tr>
<td>Serum Treated</td>
<td>4</td>
<td>6.4</td>
<td>2</td>
<td>18.5</td>
<td>3</td>
<td>3.7</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>28.0</td>
</tr>
<tr>
<td>Moderate Serum</td>
<td>45</td>
<td>16.4</td>
<td>16</td>
<td>41.4</td>
<td>20</td>
<td>7.5</td>
<td>2</td>
<td>14.5</td>
<td>16</td>
<td>13.6</td>
</tr>
<tr>
<td>Severe Control</td>
<td>11</td>
<td>16.5</td>
<td>7</td>
<td>49.6</td>
<td>2</td>
<td>8.5</td>
<td>4</td>
<td>17.8</td>
<td>6</td>
<td>19.7</td>
</tr>
<tr>
<td>Serum Treated</td>
<td>16</td>
<td>9.3</td>
<td>8</td>
<td>14.5</td>
<td>9</td>
<td>6.6</td>
<td>2</td>
<td>5.0</td>
<td>21</td>
<td>11.4</td>
</tr>
<tr>
<td>Total</td>
<td>1102</td>
<td>13.9</td>
<td>40</td>
<td>36.6</td>
<td>46</td>
<td>6.7</td>
<td>9</td>
<td>13.3</td>
<td>31</td>
<td>13.3</td>
</tr>
<tr>
<td>Serum</td>
<td>146</td>
<td>10.9</td>
<td>17</td>
<td>26.8</td>
<td>24</td>
<td>5.9</td>
<td>3</td>
<td>6.7</td>
<td>9</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Above Table by Gordon, J.E.
It has been stated that active immunization against scarlet fever has failed to achieve popularity because the procedure involves five or six hypodermic injections, and in addition, despite the fact that all the various methods have proved successful, they have not been widely accepted because of the reactions accompanying their use. Consequently many have believed that there was a need for a method of immunization which is easily accomplished, painless or nearly so and which does not cause local or general reactions. The method then proposed was based on skin absorption rather than subcutaneous or intramuscular injection of the scarlet fever toxin. The method used in this procedure was prepared by taking Dick toxin of a potency of 25,000 skin test doses per cubic centimeter, as standardized by the Michigan Department of Health, which was mixed with anhydrous lanolin so that one tube of ointment (2 ccs.) contained 25,000 S.T.D. of toxin. The toxin was freshly prepared and the ointment used within two months of its preparation.

Before administration of the ointment the patient's back was washed thoroughly with soap and water, dried thoroughly and then sponged with ten per cent alcohol. The back was allowed to dry before ointment was applied. The contents of one tube of ointment was then applied to the cleansed surface and thoroughly massaged into the tissues by hand, a rubber glove being worn by the nurse to facilitate the work and to prevent the loss of any material by absorption into her own hands.

"Two groups of children were given inunctions of the scarlet fever ointment. The first group consisted of two hundred and two children (from four to ten years of age) at the Convalescent Home of the Crip-
pled Children's Hospital of Michigan. The entire group was Dick tested to determine which were Dick positive and which were negative and those positive were used in the series. Ninety received five applications of ointment, the inundations being given every second day just before the children went to bed. No soap was applied to the back for the next 24 hours. In this group the following results were obtained:

- Total number treated (Dick positive) 90
- Total number Dick negative (six months) 42
- Total number Dick positive (in six months) 48

The second section of children were made up to a younger age group (two to six years) who were treated in the following manner:

Five applications of ointment were made with an interval of five days between the applications. Following each application, the back was massaged vigorously for five minutes.

There were 75 Dick positive children in this group. At the end of six months 61 of these were Dick negative to one S.T.D. of toxin. Four gave positive reactions and ten were not available for testing.

Comparing the two groups it would appear that the longer interval of five days and the more thorough massaging increases the number of negatives, which develop following this method of immunization. It may be that the younger the child the more easily immunized it is.

Combining the results from the two groups, from percutaneous administration of 25,000 units of scarlet fever toxin, they are as follows:
Number of cases treated..................155
Number of cases Dick positive.............155
Number of cases rendered Dick negative..103-66%
Number of cases remaining Dick positive 52-34%

In the entire series no painful or severe reactions were observed. Local reactions at the site of inunction occurred in five cases. These consisted of a fine papular eruption limited to the area. The rash usually appeared after the second dose and disappeared within thirty-six to forty-eight hours.

In one case, twenty-four hours after the third inunction, the child developed a generalized scarlatinaform rash which could not be distinguished from the true scarlet fever rash. It was limited practically to the trunk and no subjective symptoms were present. The temperature did not go above 99 degrees F. by mouth, there was no headache, nausea or vomiting and no complaint of sore throat. The throat was not inflammed. The child had had no exposure to scarlet fever. The tongue did not follow the usual course observed in most cases of scarlet fever and the patient did not desquamate. A group of three Dick positive children were intimately exposed to the child and they did not contract the disease.

It is possible that this was an extremely mild case of scarlet fever, but because of the symptoms and course it was felt to be a reaction to the application of the ointment.

It appears that scarlet fever toxin combined with anhydrous lanolin and applied percutaneously by massaging causes the Dick positive
reaction to become negative in a fairly large proportion of the cases.

The inunction method was repeated a few years later by M. L. Ripps, but in place of lanolin a cold cream base was used which proved to be superior in that it was more pleasant to handle, quicker to absorb and productive of a larger percentage of immunizations. The results are as follows:

Number of Dick positive children completing rubs........ 112
Number receiving cold cream rubs............................. 75
Number receiving lanolin rubs................................. 37
Number of Dick negative after cold cream rubs............. 46-61%
Number of Dick negative after lanolin...................... 11-29%

Giving a total of 56% for both groups. Testing after inunction was done 18 to 19 weeks later so that it is possible some of those children who remained positive at this time might later have become negative. It was also found by this worker that those children who gave the most marked reaction to the Dick test were also the most difficult to immunize.

A short time later a modification of the inunction method for active immunization was attempted by substituting the nasal route. In this method each child was instructed to rid the nostrils and nasal passageways of accumulated secretions by means of vigorous blowing. "The inoculation was then made with the child lying on its back, the chin tilted upward

The toxin was then gently sprayed alternately into each nostril, about six to eight puffs sufficed to expel the contents of the atomizer. The atomizer was a standard De Vilbiss equipped with a specially devised container which held just a trifle over 1 cc. Care was taken not to allow the tip of the atomizer to impinge on the mucosal membrane. The children were cautioned against sneezing for ten or twenty minutes following the instillation and were kept flat on their backs during this time. Needless to mention that the tip of the atomizer was sterilized between each insufflation.

"The procedure gave rise to no discomfort other than a slight burning caused by the preservative in the toxin. This complaint was trifling in nature and brief in duration and was most evident following the second instillation. No local or constitutional untoward effects were encountered. Not the slightest rise in temperature was noted. Forty children who reacted positively to the Dick test were selected from the Colorado State Home for Dependent Children. Five weekly inoculations were administered allowing a concentration of 2,000 S.T.D. for the first dose, 10,000 for the second dose, 30,000 for the third dose, 80,000 for the fourth dose and 80,000 for the fifth.

"Following the second and third instillation, nine of the older girls, domiciled in the same dormitory, complained of various symptoms, chiefly sore throat and burning in the nose. No child presented a rise in temperature. Only in one bed rest was deemed necessary. All the symptoms disappeared within forty-eight hours. Among the younger children no complaint of any kind was registered."
"Four weeks following the last instillation thirty-four children presented themselves for the retest. Of these thirty-four children fourteen or approximately 41 per cent were still positive. The Dick test was again performed six weeks later and this resulted in the reversal in four of the fourteen positive reactors, raising the percentage of the successfully inoculated to nearly 70%. Of the ten inoculated who remained positive, six showed a striking decrease in the intensity of the reaction. This doubtless means that a considerable measure of immunity had been created, however not quite sufficient to insure optimum protection."

The most recent publication on the diagnosis and treatment of scarlet fever is that of Max J. Fox, who has made the following observations in his study of 5,742 cases in the past ten years at the Milwaukee Isolation Hospital. In an attempt to show the variation in the severity of the disease, due to toxic manifestations, he has made the following clinical classifications:

1. The acute fulminating case is an overwhelming streptocooccal affair.

2. The severe scarlatina anginosa, i.e. extreme amount of exudate present in the fauces simulating a diphtheritic appearance with a high fever curve and its accompanying accessory sinus involvement.

3. The toxic case has the usual circumoral pallor, gastro-

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1. Freidman, Esetman, And Black: Active Immunization Against Scarlet Fever by the Nasal Route. The Jour. of Pediatrics. 5:504, (October), 1934.
enteritis, joint pains and exaggerated punctiform rash, most pronounced in the folds of the body.

4. Mild cases with nothing outstanding in the form of septic or toxic manifestations and the subjective and objective findings of such a character as to merit purely palliative and symptomatic treatment.

5. The traumatic and surgical cases.

There is still another group of cases that were formerly spoken of as recrudescent, but which we have concluded occur in types of individuals who lose their antibodies during convalescence and are self-infesting showing the reappearance of the entire triad of this disease.

<table>
<thead>
<tr>
<th>TABLE I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PART I - CLINICAL TYPES OF CASES</strong></td>
</tr>
<tr>
<td><strong>No.</strong></td>
</tr>
<tr>
<td>1. Malignant.................</td>
</tr>
<tr>
<td>2. Septic..........................</td>
</tr>
<tr>
<td>3. Toxic..............................</td>
</tr>
<tr>
<td>4. Mild.............................</td>
</tr>
<tr>
<td>5. Without rash.......................</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

| **PART II - SYMPTOMS** |
| **No.** | **Cases** | **Per Cent** |
| 1. Sore Throats |
| a. Severe............... | 1115 | 19.42 |
| b. Mild................ | 4627 | 80.58 |
| 2. Vomiting............... | 1373 | 24.0 |
| 3. Strawberry tongue...... | 4052 | 71.0 |
| 4. Desquamation........... | 4278 | 74.5 |
# TABLE II

## COMPLICATIONS

<table>
<thead>
<tr>
<th>No. Cases</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Cervical Adenitis</strong></td>
<td></td>
</tr>
<tr>
<td>a. Non-suppurative</td>
<td>1,209</td>
</tr>
<tr>
<td>b. Suppurative</td>
<td>78</td>
</tr>
<tr>
<td><strong>2. Rhinorrhea</strong></td>
<td>1,788</td>
</tr>
<tr>
<td><strong>3. Perleche</strong></td>
<td>977</td>
</tr>
<tr>
<td><strong>4. Sinusitis</strong></td>
<td></td>
</tr>
<tr>
<td>a. Ethmoidal</td>
<td>48</td>
</tr>
<tr>
<td>b. Sphenoidal</td>
<td>4</td>
</tr>
<tr>
<td><strong>5. Peritonsillar Abscess</strong></td>
<td>336</td>
</tr>
<tr>
<td><strong>6. Recurrent Rash</strong></td>
<td>100</td>
</tr>
<tr>
<td><strong>7. Arthritis</strong></td>
<td></td>
</tr>
<tr>
<td>a. Simple Synovitis</td>
<td>38</td>
</tr>
<tr>
<td>b. Polyarthritits</td>
<td>256</td>
</tr>
<tr>
<td><strong>8. Otitis Media</strong></td>
<td></td>
</tr>
<tr>
<td>a. Spontaneous rupture of membrane</td>
<td>495</td>
</tr>
<tr>
<td>b. Paracentesis</td>
<td>218</td>
</tr>
<tr>
<td>1. Unilateral</td>
<td>504</td>
</tr>
<tr>
<td>2. Bilateral</td>
<td>209</td>
</tr>
<tr>
<td>c. Mastoiditis</td>
<td>60</td>
</tr>
<tr>
<td>1. Operative</td>
<td>35</td>
</tr>
<tr>
<td>2. Non-Operative</td>
<td>25</td>
</tr>
<tr>
<td><strong>9. Acute Glomerulo-nephritis</strong></td>
<td></td>
</tr>
<tr>
<td>a. First week</td>
<td>9</td>
</tr>
<tr>
<td>b. Second week</td>
<td>33</td>
</tr>
<tr>
<td>c. Third week</td>
<td>39</td>
</tr>
<tr>
<td><strong>10. Heart</strong></td>
<td>147</td>
</tr>
<tr>
<td><strong>11. Lungs</strong></td>
<td></td>
</tr>
<tr>
<td>a. Pneumonia</td>
<td>52</td>
</tr>
<tr>
<td>b. Pleurisy</td>
<td>25</td>
</tr>
<tr>
<td><strong>12. Abdominal</strong></td>
<td></td>
</tr>
<tr>
<td>a. Gall bladder</td>
<td>11</td>
</tr>
<tr>
<td>b. Appendicitis</td>
<td>7</td>
</tr>
</tbody>
</table>
In relation to antitoxin treatment, Dr. Fox states: "It has been our experience that when a case is definitely toxic, showing a mouth temperature of 102 degrees or more, characterized by gastro intestinal symptoms and a marked rash, one therapeutic dose (antitoxin neutralizing 300,000 skin test doses) was not sufficient and we always resorted to two therapeutic doses. Six cases of a severe septic character were given blood transfusions from patients that had convalesced within a period of ninety days. These patients showed evidence of marked sinus sepsis with usually some meningeal irritation. It was necessary in two patients, during convalescence, where no serum had been given during the acute stage, to resort to immuno-transfusions after the development of severe septic findings."

Dick tests are done routinely on all patients entering the hospital and a blanching test is routinely done on all patients still having a rash. The results of this procedure are as follows:

<table>
<thead>
<tr>
<th>TABLE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blanching Tests:</td>
</tr>
<tr>
<td>a. Negative................. 971</td>
</tr>
<tr>
<td>b. Positive.................. 565</td>
</tr>
<tr>
<td>2. Dick Tests:</td>
</tr>
<tr>
<td>a. On Entrance Negative........ 2328</td>
</tr>
<tr>
<td>b. On Entrance Positive........ 484</td>
</tr>
<tr>
<td>3. Fourth Week Release Throat Cultures.</td>
</tr>
<tr>
<td>a. Negative................. 2675</td>
</tr>
<tr>
<td>b. Positive.................. 331</td>
</tr>
</tbody>
</table>

Of the 484 positive Dick tests on entrance, ten days later 128 were still positive and twenty days after admission 46 remained positive. From the above findings Dr. Fox states that: "This observation would imply that the majority of scarlet fever cases develop a negative Dick test within a few days after the onset of the ailment. Hence, this biologic test cannot be considered a reliable measure to decide if a given case is a resultant from the streptococcus of scarlet fever. In the final analysis the clinical picture remains the deciding factor in making a positive diagnosis. Blanching tests (Schultz-Charlton reaction) were done in 1536 cases, 971 were negative, 565 were positive. This biologic toxin-antitoxin phenomenon is only diagnostic when positive and the same conclusion must be reached concerning the value of the Dick test. It is merely a corroborative finding and should be given the same interpretation as the 1 Wassermann test in Syphilis."

"The time when a patient after scarlatina is no longer dangerous to his surroundings chiefly depends upon the severity of the course of the disease. An accurate inspection of the throat and precautions if there is still a swelling of the cervical glands no matter how slight are of paramount importance. The squamae are primarily not contagious, but are so if they come into contact with infectious pharyngeal mucus. Mild cases can usually be discharged from quarantine after twenty-eight days, provided the temperature has been normal for five to six days and the palpation of the neck is negative. Shortly before releasing the patients, two urinalysis must be made. Cases with a severe course from the onset must fre-

1. Ibid
quently be quarantined for more than forty days. The release depends
upon the clinical findings. It is not necessary to make pharyngeal
1
smears."

During the last two decades, scarlet fever mortality has shown
a marked downward trend in practically all the countries of the world.
During the same period, however, the morbidity rate has remained more or
less stationary. Because of the occurrence of so many mild cases of
scarlet fever and a comparatively low death rate at the present time,
there is a tendency on the part of many people, including a considerable
percentage of physicians, to look upon this disease rather lightly. As a
matter of fact, those properly informed still regard scarlet fever as one
of the most dreaded diseases of childhood, not only because an acute
attack may be so malignant as to cause death in a short time, but mainly
because of the many and grave sequellae and complications with which it
may be attended. The death rate charted against scarlet fever tells but
a small part of the story. Attestation of this fact is coming more and
more frequently from physicians who are being called upon to treat otitis
media, mastoiditis, sinusitis, heart and kidney diseases, puerperal sepsis,
wound infection and various other afflictions associated with or following
2
scarlet fever infection.

It is partially for this reason and also because of the growing
trend to practice preventive medicine that communities, local medical

1. Marfan, A.E.: How Long Must The Patients with Scarlatina be
From paper given before Milwaukee Med. Assn. 1934.
associations and public health associations are endeavoring to establish an immunization and public health control program for scarlet fever in their respective localities. This work, however, is still in its infancy and while at the present time many localities are carrying out this program many have neglected to keep accurate statistics of the work done and the results obtained, while many of those who have kept an accurate record are not as yet able to publish with any degree of accuracy, the results of their work.

A considerable amount of this work has been carried out in Kentucky in the past five years and they have endeavored to promulgate an effective, scientific procedure in its control as shown in the following report:

"In March, 1929, an epidemic of scarlet fever occurred at Berea College, Berea, Kentucky, with 414 cases among the student body of 2000. Up to this time, it had been our custom in Kentucky, as is still the case in so many places, to depend entirely upon quarantine and isolation, realizing all the while however that such control measures were inadequate. At the same time we had, it is true, a limited knowledge of active and passive immunization against this disease, but we were quite un-convincing of its efficacy.

After due consideration of all aspects of our problem the following general program of control was decided upon:

1. Pasteurization of the college milk supply
2. Isolation of all cases in the college hospital or in
dormitories set aside for the purpose.

3. Campus quarantine of all persons connected with the college, based on the results of nose and throat cultures taken on blood agar plates.

4. Skin tests taken on all persons connected with the college to detect susceptibles.

5. Active immunization of all susceptible persons with the five graduated doses of scarlet fever toxin.

Although this epidemic promptly subsided within ten days following the initiation of this program, it is not our contention that the carrying out of these measures merits the entire credit for this accomplishment. The outbreak was milk-born, explosive in type, and naturally would have subsided following protection of the milk supply. It is our firm conviction, however, that had we not followed through with the culturing and immunization program, the disease would have continued to smolder, with the sporadic occurrence of many cases during the remainder of the school year. It has been our repeated observation that this invariably happens whenever we depend on isolation and quarantine alone.

Of the four hundred and fourteen cases, three hundred and fifty were Dick tested during the early stages of the disease and all were found positive. While a majority of these cases were relatively mild, it was constantly observed that the size and intensity of the reactions were in more or less direct proportion to the severity of the attack. These three hundred and fifty patients were again Dick tested and all but three now had negative reactions.
Of the 2,308 persons Dick tested at Berea, 852 or nearly 37 per cent were positive. Immunity to scarlet fever will vary according to age and previous exposure to infection. This was shown very clearly in this study. Among the 2,308 individuals tested there were thirty-seven faculty children of pre-school age, with 97 per cent susceptible; 137 training school children, ranging in ages from six to fourteen years, with 60 per cent susceptibility, and 2,134 adults with a susceptibility of 34 per cent.

Cultures were made on 2,296 persons at Berea, 898 or 39 per cent of whom were positive. However, of the eight hundred and ninety-eight, four hundred and fourteen were patients in the hospital with scarlet fever. That is, all the patients with scarlet fever regardless of how mild their symptoms were had positive cultures. Leaving this group out of consideration there remained 1,882 on whom cultures were taken, four hundred and eighty four of those, or 25.7 per cent, being positive. Among the four hundred and fourteen cases a rash recognized in only eighty three, or a little over 20 per cent.

It is frequently claimed that the normal throat harbors hemolytic streptococci. To check the results obtained at Berea against a control group, the throats of students at Eastern State Normal School at Richmond, Kentucky, were cultured. A few sporadic cases of scarlet fever had been reported in the city of Richmond, but none from among the college students. These students had essentially the same background and age distribution as those at Berea College. Of a total of seven hundred and eighty six cultures but forty seven or 6 per cent were positive as compared with 39 per
cent at Berea. Since that time hundreds of thousands of cultures for the
detection of hemolytic streptococci have been made in Kentucky, under a
great variety of conditions, and it has been our repeated observation
that the percentage of "carriers" in any group is more or less in direct
proportion to the number of cases of scarlet fever present.

In May, 1929, shortly after our experience at Berea, the State
Board of Health was notified of an outbreak of puerperal sepsis in one of
the hospitals at Lexington. An investigation of this situation disclosed
the prevalence of scarlet fever at this institution. At the time two
nurses were in bed with moderately severe and typical attacks of the di-
sease, and it was learned that there had been three other definite cases
among nurses during the preceding six weeks. Upon culturing the hospital
staff, nurses and attendants, one hundred and twenty in all, it was found
that twenty-four, or 20 per cent, were carriers of hemolytic streptococci.
The organism obtained from each of these carriers was later identified by
means of specific toxin production as belonging to the scarlet fever strain

During the month previous to this investigation, five patients
in this hospital had died from puerperal sepsis. In four the offending
organism has been identified as a hemolytic streptococcus. In the other
case the causative agent was not determined. Unfortunately, at the time
of this study, cultures of these organisms were not available. Hence, it
was not possible to identify the strains of hemolytic streptococci respon-
sible for these deaths.

On further investigation it was learned that one of the nurses,
ill at the time with scarlet fever had attended three of the patients who
died and that all five of the dead patients had been attended at some time
during the delivery or the puerperium by from one to five of the nurses
who were found at the time of the study to be carriers of scarlet fever
germs.

The epidemiological evidence evolved through this study definite-
ly indicates that these cases of puerperal sepsis were due to the scarlet
fever streptococcus, transmitted through the agency of carriers. Follow-
ing active immunization of all suspects and isolation of all carriers, the
outbreak of scarlet fever promptly subsided.

During the summer of 1929 representatives of the State Board of
Health went to Clay, Kentucky, a small mining community of about 3,000,
to assist the physicians and health authorities in controlling a wide-
spread outbreak of scarlet fever in that community. Essentially the same
program which had been carried out at Berea was instituted there. An
additional interest, however, presented itself in this study in that an
immunization program, using a preparation known as "recinoleated antigen"
had previously been carried out by the local physicians and yet many of
these so immunized continued to develop scarlet fever.

A thorough study of "recinoleated antigen" disclosed not only
that it failed to immunize, even temporarily, but that in addition its use
was followed by severe reactions. This preparation has since been con-
demned by the National Institute of Health and it has been taken off the
market.

At Clay about 2,000 persons, adults and children, were cultured
and Dick tested. 38 per cent were found to be carriers of hemolytic streptococci and 24 per cent had positive tests. Of the susceptible group over 87 per cent were completely immunized. This outbreak which had been going on for months, and which unlike the one at Berea was contact born, completely subsided within three weeks following the institution of this program.

During the past five years, following the outbreak at Clay, the State Board of Health has been calling upon to assist a number of communities and institutions in the state with outbreaks of scarlet fever. In each instance, our program has been essentially the same. Up to July of this year about 200,000 skin tests and 30,000 complete immunizations had been given and upwards of 300,000 throat cultures have been made under the supervision of the State Board of Health, working in cooperation with our fulltime health departments. In addition, numerous physicians in various parts of the state have been gradually taking up the work, so that at present the aggregate experience probably exceeds that of the State Board of Health.

As regards the duration of the immunity following the administration of five dose series of scarlet fever toxin, experience to date indicates that it is comparable to that in diphtheria following the use of toxin-antitoxin. The present method of immunization has only been in use for about nine years, but repeated skin tests on a large series, carried out under the supervision of the Dicks over this period of time, seems to indicate that over ninety per cent continue to retain their immunity.

Our experience in Kentucky has as yet been rather limited in
this connection. It is our purpose to go ahead with a retesting program, covering a period of years, among those completely immunized. To date but four hundred and fifty of those immunized have been retested. Of this number, two hundred and forty seven were retested two years after inoculation with the five graduated doses of scarlat fever toxin, and one hundred and three were retested four years after such immunization. Of the two hundred and forty seven retested in two years, 94 per cent continued to have negative skin tests; of the one hundred and three retested in four years, 91 per cent were negative. Furthermore, of the two hundred and forty seven retested at the end of two years, one hundred and sixty two were again retested at the end of four years and one hundred and sixty, or 98.7 per cent, had remained negative."

Dr. Jones states in conclusion that in their series "of some 60,000 complete immunizations carried out during the past five years, there has, as yet, been no case of scarlat fever officially reported".

The most recent result available of a large scale immunization program is that of the Health Department of the City of Milwaukee, which completed a course of Dick testing and immunization work on 10,000 school children. The following is abstracted from their January 1935 report to the City Council.

Milwaukee in 1934 when it was threatened with an epidemic of scarlet fever started an immunization program in a few of its public and private schools. The schools chosen were those which were highly infected. This program was carried out more for its informative value than as an attempt to check a city-wide epidemic. Dick testing was done on 10,000 school children to discover susceptibles. The positive reactors were started with five doses of toxin, as recommended by the Dicks, namely 500, 2000, 8,000, 25,000, and 80,000 skin test doses at weekly intervals. At the same time, immunization was offered by many private physicians as well as the Health Department. As other schools were infected more of this work was carried on, so that from March 12 to July 1st, 12,656 Dick tests were given; 12,347 read; 8,272 or 67% were positive and 4,075 or 33% were negative.

The results varied a great deal. The younger the child the more liable it was to be positive. The more crowded the neighborhood in which it lived, the more liable was the test to be negative.

Of the 8,272 positive reactors, only 6,516 started the immunization program with the Dick toxin. 5,834 reported for the second injection, 5,359 for the third injection, 4,602 for the fourth injection and 4,001 or 60% completed the course of five injections. A sixth injection was given to 141.

The following table gives a summary of the reactions which occurred as obtained by interviewing pupils, teachers, parents and nurses.
MILWAUKEE HEALTH DEPARTMENT

SCARLET FEVER IMMUNIZATION
(Including Schools)

March 12th, 1934 to June 30th, 1934.

**DICK TESTS**

<table>
<thead>
<tr>
<th></th>
<th>Before Immunization</th>
<th>After Complete Immunization</th>
<th>After Incomplete Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Tests Given</td>
<td>12,656</td>
<td>3,584</td>
<td>1,088</td>
</tr>
<tr>
<td>Total Tests Read</td>
<td>12,347 -98%</td>
<td>3,511-98%</td>
<td>1,051 - 97%</td>
</tr>
<tr>
<td>Positive</td>
<td>8,272 -67%</td>
<td>194- 6%</td>
<td>376 - 36%</td>
</tr>
<tr>
<td>Negative</td>
<td>4,075 -33%</td>
<td>3,317-94%</td>
<td>675 - 64%</td>
</tr>
</tbody>
</table>

**TOTAL SCARLET FEVER TOXIN INJECTIONS**

- First injection - 6,516
- Second injection - 5,834 - 90%
- Third injection - 5,359 - 82%
- Fourth injection - 4,602 - 71%
- Fifth injection - 4,001 - 61%
- Sixth injection - 141 - 2%
- Seventh injection - 1
- Total - 26,454

**REACTIONS**

<table>
<thead>
<tr>
<th></th>
<th>Systemic</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
<th>Total</th>
<th>Local Reaction</th>
<th>No Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1st injection</td>
<td></td>
<td>2%</td>
<td>8%</td>
<td>11%</td>
<td>21%</td>
<td>33%</td>
<td>46%</td>
</tr>
<tr>
<td>After 2nd injection</td>
<td></td>
<td>2%</td>
<td>13%</td>
<td>14%</td>
<td>29%</td>
<td>22%</td>
<td>49%</td>
</tr>
<tr>
<td>After 3rd injection</td>
<td></td>
<td>4%</td>
<td>19%</td>
<td>18%</td>
<td>41%</td>
<td>18%</td>
<td>41%</td>
</tr>
<tr>
<td>After 4th injection</td>
<td></td>
<td>4%</td>
<td>19%</td>
<td>19%</td>
<td>42%</td>
<td>21%</td>
<td>37%</td>
</tr>
<tr>
<td>After 5th injection</td>
<td></td>
<td>2%</td>
<td>14%</td>
<td>21%</td>
<td>37%</td>
<td>21%</td>
<td>42%</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>3%</td>
<td>15%</td>
<td>16%</td>
<td>34%</td>
<td>23%</td>
<td>43%</td>
</tr>
</tbody>
</table>

**Severe Systemic** - 102 temperature, severe prostration or coma for a period of hours, vomiting, diarrhea with bloody stool.

**Moderate Systemic** - Slight degree of lassitude with some mild rise in temperature; possibly slight nausea or vomiting, muscular involvement, rash.

**Mild Systemic** - Slight degree of lassitude or rash

**Local Reaction** - Redness and swelling of arm and limitation of motion with various degrees of discomfort resulting therefrom.
RESULTS OBTAINED

Immunity conferred by Dick scarlet fever toxin as evidenced by second Dick tests two weeks after the fifth injection and from two to six weeks after incomplete courses of treatment were approximately as follows:

First injection .................. 10%
Second injection .................. 20%
Third injection .................. 40%
Fourth injection .................. 80%

The average was 63%. Those who had five or more injections were 93% Dick negative.

Sixteen children receiving only one injection of scarlet fever toxin developed scarlet fever. One child with two injections and one with only three injections acquired scarlet fever. Those having four or more injections did not contract the disease.

Although there was a steady increase in the proportions of the scarlet fever epidemic throughout the schools in the city, it did not increase in those schools where immunization work was done. The immunization of 3,000 to 4,000 school children out of an enrollment of 37,000 cannot be expected to check a city-wide scarlet fever epidemic.

One school in which 76% of the children were either immunized or had a preliminary negative Dick test had 31 cases reported before and up to the time of the third injection and not one after that. With one exception only all schools showed a marked decrease in scarlet fever after the
first and second doses of scarlet fever toxin. The one exception was a
school where a good many of the children refused the Dick test or the
positive reactors refused immunization.

PRECAUTIONS TAKEN

1. Every child was given a medical examination before the first dose of
scarlet fever toxin was administered.

2. Every child's temperature was taken before each dose of toxin was ad-
ministered, to exclude those that were ill. At first 99.6 degrees was
the maximum permissible, but this temperature was so common in children
that the maximum was raised to 100 degrees F.

3. Whenever possible, all immunizing work was done in the afternoon as some
of the children immunized in the morning became sick and vomited in the
classroom, thus upsetting the whole group.

4. When done in the morning the school nurse stayed on duty at the school
in the afternoon.

5. A doctor and a nurse were in the school the following morning for in-
specting rashes and other reactions.

6. Printed notices were given to the parents after the first injection
advising them of some of the reactions that might occur and assuring
them that there was no cause for alarm.

7. Every child absent from school following an immunization treatment was
visited by the school nurse.

8. Since all children recover from reactions, no matter how severe, it is not necessary for the nurse to follow up cases in home.

9. Cultures taken on 2,693 children in 35 schools and of this number 902 were positive for hemolytic streptococcus and the children were excluded from school for one week. Children with negative cultures in school developed scarlet fever about as fast and as frequently as did those that were excluded.

CONCLUSIONS

1. Scarlet fever toxin does cause reactions, some of which are severe.
   About thirty per cent of all children develop a rash after one injection.

2. All children recover completely from the reaction and nearly all of them in twenty four hours.

3. Parents do not worry about reactions if forewarned. They are more eager to accept immunization for scarlet fever than almost any other disease. This is due to the uncertainty of the disease as well as the long quarantine period.

4. Health officers and private physicians who have not complete confidence of school authorities and parents should not attempt scarlet fever immunization, because the reactions occurring might frighten people and jeopardize the whole immunization program as well as the reputation of
the health officer or the family physician.

5. Five injections of Dick scarlet fever toxin changes a positive Dick to a negative Dick test in 94 per cent of all cases. Nearly one hundred per cent of all children receiving two or more injections of scarlet fever toxin appear to be immune, at least temporarily to scarlet fever.

6. Scarlet fever immunizations conducted on a large scale cost approximately $2.50 a person including material, medical care, nursing and clerical service for the two Dick tests and the five injections of scarlet fever toxin. Two Dick tests and their reactions interfere considerably with school work. When the cost of immunization is compared with the cost of medical and nursing care of the scarlet fever patient in the home and isolation hospital, as well as with the economic loss due to quarantined homes, the cost of immunization is still cheaper than the treatment of the disease.

7. The interference with school work over a long period of time will be less with the expeditiously conducted immunization program than it will be to continue to permit a large percentage of school children to contract scarlet fever annually,
In conclusion, as shown by the literature, scarlet fever is a relatively ancient disease, being first described by John Philip Ingrassias in the sixteenth century. There was, however, relatively little progress made in the etiology and treatment until after the World War when Dochez, Schultz-Charlton, George and Gladys Dick and others established the streptococcus scarlatinae as the etiological agent and developed the Dick test to determine susceptibility to the disease. From these findings investigators were able to develop immunization procedures by intramuscular injections, inunctions and insufflations with the toxin produced by the organism, and to develop an antitoxin to treat the malady. Schultz and Charlton formulated a blanching test with the antitoxin to aid in the diagnosis of scarlet fever. The value of the Dick and blanching tests, however, are only of diagnostic significance when positive, and should only be considered as corroborative findings.

On the basis of these discoveries the present control of scarlet fever has been advocated, in which active cases and those individuals with positive throat cultures are isolated, contacts quarantined and Dick positive, or susceptible individuals, are actively immunized.

Although there has been a tremendous advancement made in the field of scarlet fever in the past decade and a half, it is our belief that the problem still presents an unlimited opportunity for study, and that more efficacious methods for its control and treatment are yet to be learned.
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Approved by

[Signature]
Professor of Medicine

Date

April 16, 1935