THESIS

on

ANTISTREPTOCOCCUS SERUM

ITS APPLICATION IN THE TREATMENT OF SCARLATINA ANGINOSA

by

CAMPBELL SAMSON MARSHALL, M.B., C.M., D.P.H. (Camb.)

Western Typewriting & Shorthand Office,
118 West Regent St., Glasgow.

Within recent years, owing to the advance made in our knowledge of micro-organisms, and the products of their vital activity - due to the perfecting of the methods of bacteriological research and investigation - a new phase of medical treatment has been inaugurated, viz: serum-therapy. This mode of treatment is applicable, in the widest sense, to all those diseases which have a microbic origin, and in which a serum, either antitoxic or anti-microbic in nature, can be obtained from an animal which has been rendered immune, by various methods, to the disease-producing micro-organism. These methods are manifold, but their ultimate result is the same, i.e. the formation of a serum which has an inimical influence either on the microbes or on their toxines. The results which have attended the use of antidiphtheritic serum have encouraged bacteriologists to pursue their investigations of the biology of other organisms, and a number of sera are now manufactured which are claimed by their respective discoverers to have certain specific effects. Examples

of these are to be found in the serum of tetanus, cholera, bubonic plague, yellow fever and streptococcal infections. The beneficial effect of antidiphtheritic serum is admitted by most observers, but sufficient trial has not been given to the other sera mentioned to warrant a definite expression of opinion. Encouraged by the good results in a small number of cases treated by these sera, there has been a tendency to form hasty generalisations, and an attitude is assumed which is not justified by the number of facts collected. More especially in regard to anti-streptococcus serum much harm has been done, and the issues have been confused by a want of the scientific application of the serum. This has also been felt in cases of diphtheria combined with a streptococcal infection, where, in spite of manifest improvement in the local condition of the throat from the use of antidiphtheritic serum, the patient has often succumbed to streptococcal intoxication. The application of all sera should be directed against a particular organism, and just in proportion as the infection is a mixed one, so we should expect, unless a compound serum is used, to find our results unsatisfactory.

While, from the laboratory point of view, it would be difficult to give precedence to the study of any one

micro-organism and its toxine, from the purely clinical standpoint the study of the biological characteristics of the streptococcus, so potent in its pathological effects, will always hold a foremost place. It is probably the most widely distributed form of microbic life: it is more variable in its morphological development than any of the others: it is unequal in the matter of biological characteristics, and is the most far reaching in its pathogenic effects.

The difficulty of attributing any definite pathology to the streptococcus, and its association in so many dissimilar diseased conditions, such as erysipelas, puerperal fever, septic wounds, diphtheria and scarlet fever, readily accounts for the wide diversity of opinion that exists, among various observers, as to its nature and effects.

Until quite recently, bacteriologists had taken the view that in all the above mentioned diseases there was a distinct species of streptococcus concerned. Indeed as many as twelve different species of streptococci have been described. Especially was a sharp line of distinction drawn between the streptococcus erysipelatis of Fehleisen described by that investigator in 1883, and the streptococcus pyogenes of Rosenbach described in 1884.

Within the last five years, however, these views

have been abandoned, and Continental, American and British observers, with the one notable exception of Klein in this country, are now almost unanimous in their belief in the unity of the streptococcal germ, so far at least as toxine formation is concerned.

Unity of Streptococcal toxine

The difference in size, form, and effects of cultures of streptococci may be accounted for by the environment of the organism. These characters may vary according as the germ is cultivated on natural or artificial media, or even on different natural or artificial media according to their origin. Thus it was found in the cultivation of the streptococcus, that in some instances the loops were long and twisted with an extremely high degree of virulence; in others they were short and straight and comparatively innocuous in their effects. This led to the belief that the long streptococci were always very virulent, and the short chains harmless. Marmorek, however, by injecting the same culture into rabbits and mice found that in subcultures from the blood of the former animal the chains were longer and in the latter were shorter, although the virulence remained the same in both. By inoculating other animals, the same facts were brought out. As another proof of his contention, he offers the

further experimental fact that streptococci from various sources, and of varying grades of virulence, may, by successive cultivation in the bodies of animals, all be brought to a point of virulence identical, all producing in animals an acute septicaemia. In a report of his work in this line, published in the "Annales de l'Institut Pasteur July 1895," he sums up in these words, "nos expériences confirment l'opinion de ceux qui regardent toutes les affections streptococciques de l'homme comme dues a un microbe unique."

Petruschky has collected a number of streptococcal affections of man, and submitted them to accurate bacteriological examination. He concluded that various streptococcal conditions pass one into the other, or proceed from one another. This observer adduces the case of an infant who suffered from a typical attack of erysipelas from a scratch in the naso-labial fold. The mother suffered from mastitis which, however, showed no erysipelatous character.

Why a streptococcus should produce in one case an abscess, in another case erysipelas, and in a third pyaemia, is probably attributable partly to differences in virulence, resistance capacity, and partly to the seat and mode of entrance into the body.

The general recognition of the unity of the strepto-

coccus microbe warranted the belief that the first step had been reached in the preparation of an antitoxin. The chief difficulty consisted in the inability to produce a potent filtered streptococcus toxine; for, while there is good reason to believe that some soluble poison of a very powerful nature is produced in the bodies of infected persons, yet the filtrates of cultures of streptococci have but little toxic action. Recently Roger has succeeded in immunising rabbits by injecting filtered cultures heated to 120° C., but no attempt has yet been made to produce an antitoxin.

Having settled in his own mind the question of the unity of the germ, Marmorek next proceeded to endeavour to prepare a serum which would destroy it. Roger, Behring, Mironoff, and Lingelsheim had succeeded in establishing many points of interest in connection with the development and effects of the germ itself, and had even prepared a serum that was partially successful in destroying it. However, these observers never succeeded in preparing a serum of sufficient potency to act effectively upon the severer forms of the infection.

It has been clearly demonstrated that "laboratory sera," such as were formerly made by employing a selection of members of the rodent family, are so attenuated as to be almost inert. Such animals do not seem to be

able to resist the toxic effect of repeated injections, and hence the serum procured from them is not of sufficient potency to act with much, if any, effect on the germ. This seems to have been the difficulty with the sera made by the four observers above mentioned. Marmorek, recognising this difficulty, suggested that larger animals should be used in the preparation of the serum. This observer first used the sheep, then the ass, and latterly the horse. The horse tolerates large doses of the unfiltered toxine remarkably well, and yields by far the largest quantity of serum of any animal yet tried.

Marmorek considered that in the preparation of the serum (1) it was necessary to exercise good judgment in the selection of animals; (2) to properly care for them during their treatment; and (3) especially to avoid a too early withdrawal of the blood.

In the preparation of antistreptococcus serum, as is the case in the preparation of products of like character, time, skill, and experience are required, and sera manufactured carelessly, and with a lack of one or more of these factors, have been put on the market, and have led to failure and disappointment in their use.

The process of manufacture is necessarily a slow one, and a horse requires to be under treatment at least a year

before the serum reaches its maximum antistreptococcic strength. The blood of the animal must not be withdrawn till some time after the last injection has been made, as during the reaction the blood is actually toxic, and, if injected into rabbits during this time, will invariably kill them in from five to ten days. At the British Institute of Preventive Medicine Horse Farm at Sudbury, where the author recently had an opportunity of examining the animals and seeing the main points in the process of manufacture of the serum, the modus operandi is as follows, viz:- 50 ccs of a serum bouillon culture of a streptococcus derived from an acute abscess and a streptococcus from a fatal case of septicaemia are usually injected. Previous to 1898 the serum prepared was "univalent." The streptococcus of erysipelas was employed, its virulence being enhanced by Pasteur's method of passage through rabbits. All the cases of Scarlatina Anginosa in the subsequent series were treated with a serum prepared in this manner.

Cases in subsequent series treated with "univalent" serum

After the injection of the culture, the temperature rises steadily till in six or seven hours 41° Centigrade (105.4° Fahrenheit) is registered, 38° Centigrade being the normal temperature of the horse. A decline then sets

in, and the temperature is usually normal the following day. At various periods samples of blood are drawn to estimate the preventive and curative power of the serum, and also to determine the length of time during which the serum remains toxic after inoculation. According to experiments made at the British Institute of Public Health, the serum does not remain toxic for so long a period as that found by Marmorek in his investigations. A month is allowed to elapse between the last injection and the withdrawal of the blood from the horse. The serum is preserved by being kept cold, and no antiseptics are added for this purpose. Roux, who has had a large experience in the manufacture of antitoxins and sera, asserts that antiseptics can do no possible good, and are capable of doing a great deal of harm. The sera, in his opinion, are not preserved by antiseptics, as is popularly supposed: they will only keep a certain time: they must be kept at a proper temperature in order to retain their vitality, and, if so kept, will remain potent as long without antiseptics as with them.

Up till recently, and long after the author began to use the antistreptococcus serum in anginous scarlet cases, the question of the unity of the streptococcal germ was accepted in all its entirety, whether viewed from the

morphological or biological aspect. Lately, however, certain experiments have been made by observers whose results are so unanimous, and cannot be contradicted, that the question in one of its aspects at least is re-opened. These experiments have shown that whereas a serum of a horse immunised against a certain streptococcus will protect the animal against the streptococcus used to immunise it, there is no protection conferred on the animal against a streptococcus derived from a different pathological condition.

Although the ultimate identity of streptococci from various sources cannot be doubted, yet there seems to exist a subtle distinction in the bactericidal substances which streptococci, associated with different pathological manifestations in the human economy, produce in the blood of animals into which they are injected.

The most interesting experiments in this line were made by Van de Velde. This investigator selected two streptococci A and P, both of which when injected into a rabbit's ear produced erysipelas without any streptococci being found in the blood and internal organs. With each of these microbes he immunised a horse and obtained two sera. The serum obtained from horse A protected against streptococcus A, but had a very feeble protecting influence against streptococcus P. The serum obtained from

horse P protected against streptococcus P, but failed to protect against streptococcus A. This experimenter also went one step further. Having injected 5 cubic centimetres of each of these sera (A and P) into two rabbits, he inoculated the right and left ears of these animals with streptococcus A and P respectively. In the rabbit injected with serum A only the ear inoculated with streptococcus P developed erysipelas, while the converse occurred in the case of the other animal. The position which this observer takes up was still further strengthened by the fact that he immunised a horse with both streptococci A and P, and obtained a serum which would protect against both these organisms. From these results he recommends that animals employed to yield serum should be injected with a number of streptococci from various sources in the hope of obtaining a serum active in its bactericidal properties against as many streptococci as possible.

This observer also investigated the agglutinating power of his sera, and he finds that it is always in direct proportion to the power of protecting. Thus, in his experiments quoted above, he found serum A agglutinated streptococcus A, and serum P agglutinated streptococcus P, and that serum A + P agglutinated both.

The outcome of these experiments was the suggestion that the patient's blood should be tested against a number of streptococci, to get some idea of its agglutinating power. These streptococci could have corresponding sera. In this way having found the streptococcus which was best agglutinated by the patient's blood, the serum could be selected which would probably have the most beneficial effect in stemming the progress of the disease.

The practical conclusion arrived at by this observer was that each variety of streptococcus was able to produce in the animal, into which it was injected, a particular antimicrobic body which was inimical to the life of that streptococcus. This statement is not an exclusive one, and an antimicrobic serum, which did not correspond to a particular variety of streptococcus, might have an influence on that organism, although not to such an extent as on the corresponding streptococcus.

These facts open up a very important aspect of the case in regard to the practical application of the serum in human disease.

The difficulty of preparing a potent germ-free toxine of a streptococcus has been adverted to previously. All experiments in this line have therefore been conducted with an antimicrobic, and not with an antitoxic, serum.

The author was much impressed by the want of uniformity which attended the use of the serum even in cases which seemed in all respects comparable to one another. The argument would therefore be urged that in scarlatina anginosa there may be different varieties of streptococci present so far as their vulnerability to the bactericidal substances contained in the serum is concerned, and that, according to this, did improvement take place or not.

Although different races of streptococci require a corresponding bactericidal serum, and are affected to a modified degree only by other sera, yet the toxines produced by the various streptococci may be essentially of the same nature, and it seems reasonable to hope that they may be counteracted by a single antitoxin.

The researches of Calmette lend support to these suggestions: for he has shown that the poisons of the most varied serpents, and also of the scorpion, while they differ somewhat in their action upon animals, nevertheless are counteracted by one antivenin.

Bearing these considerations in mind it seems that our aim should be to produce, if possible, an antitoxic rather than an antimicrobic serum for the treatment of diseases caused by streptococci.

That there is good reason to believe that the bactericidal substances formed in the bodies of the animals, into which different forms of streptococci are injected, are varied, is proved by Renou's observations in cases of scarlet fever. This investigator obtained a streptococcus from the blood of a scarlet fever patient. Tested on mice and rabbits successfully inoculated by this infection, it was absolutely unaffected by Marmorek's serum. The same serum, however, checked the growth of a streptococcus obtained from Marmorek, and this streptococcus was a more virulent one than that from the scarlet fever case, so that it could be inferred that streptococci of various kinds were found in man as well as in animals, some of which are subject to Marmorek's serum, and others are not. Mery also succeeded in isolating, in cases of scarlet fever, seven varieties of streptococci obtained from the throat, urine, blood and glandular abscess. Six of these streptococci proved refractory to Marmorek's serum.

The specific materies morbi of scarlet fever has not yet been discovered. Some observers have described a parasite in the blood of patients, similar in some respects to the malarial parasite. Klein in this country has described a streptococcus which he has recovered from

the blood, and also from the tubuli uriniferi of the kidneys. This observer has obtained the same organism from the teats of a number of cows supposed to be concerned in an outbreak of scarlet fever at Hendon. These opinions have not yet been confirmed, and are, in fact, strongly controverted by many competent observers in this country, so that the question must still be regarded as an open one.

Sternberg in his "Text Book of Bacteriology 1897" says "The specific infective agent in scarlet fever has not been demonstrated. In the diphtheritic exudate, frequently seen in the angina of scarlet fever, a streptococcus is commonly found which appears to be identical with streptococcus pyogenes: and in the secondary infections which occur in the course of the disease, or during convalescence when suppuration occurs; one or other of the common pyogenic micrococci are usually found, and is doubtless the cause of the local inflammatory process."

The question of the etiological factor in scarlet fever may long remain doubtful, but this, in the author's opinion, should not tie our hands in the treatment of the severer forms of the affection. All the severe complications such as pseudomembranous angina, otitis media, endocarditis, and nephritis are due to the presence of strepto-

cocci.

Stripped of these complications, scarlet fever would not be a dangerous disease. It was with these facts in mind that a justification was found, in his opinion, for an extended trial of the new serum that was introduced into the treatment of this affection.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
	SERIES NO. I. CASES IN WHICH THE THROAT SYMPTOMS WERE				
I	4	3rd	BI	10 ccs.	Streptococci very abundant, staphylococci also present.
II	9	6th	BI	10 ccs.	Both streptococci and staphylococci present, the former very abundant in nasal discharge.
III	6	11th	BI	20 ccs.	Streptococci very abundant in throat. Staphylococci also present.
	SERIES NO. II. CASES IN WHICH THE THROAT				WITH GREAT
IV	8	16th	BI	60 ccs.	Staphylococci, Diplococci and Streptococci present in throat and mouth. Diplococci very abundant in ear discharge.
V	$5\frac{10}{12}$	4th	BI	30 ccs.	One or two small chains of streptococci from gelatin culture. Practically a pure culture of staphylococcus pyogenes aureus.

REMARKS

PROMINENT, BUT WERE NOT ATTENDED WITH EXCESSIVE DEPRESSION.

Rash somewhat patchy over arms and legs. Deep ulcers with unhealthy looking edges over both tonsils and pharyngeal wall. No ulceration in front of the anterior pillars of the fauces. No nasal discharge. Slight bilateral cervical adenopathy.

Bright scarlet rash over trunk and extremities, somewhat patchy over buttocks. Ulceration over both tonsils and uvula. Sero-purulent nasal discharge. Anterior segment of mouth clean and free from ulceration. Moderate bilateral cervical adenopathy.

Throat very dirty with ulcers on dorsum of tongue and inside of cheeks and gums. Profuse sero-purulent nasal discharge. Double otorrhoea. Moderate bilateral cervical adenopathy.

SYMPTOMS WERE PROMINENT AND WERE ATTENDED

DEPRESSION

Rash patchy over buttocks and lower extremities. Throat extensively ulcerated, implicating tonsils, anterior pillars of the fauces, uvula and pharyngeal wall. Profuse semi-purulent nasal discharge. Moderate bilateral cervical adenopathy. Right otorrhoea. Death on 30th day of illness.

Frank punctate scarlatinal rash over both trunk and extremities. Throat is extensively ulcerated. Profuse nasal discharge. Ulceration proceeded very rapidly as evidenced by marked huskiness and dysphagia. Slight cervical adenopathy. Septic rash on 8th day of illness over elbows, knees and ankles. Death on 11th day of illness.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
VI	7	5th	BI	20 ccs.	Streptococci, staphyllococci and a short rod (probably bacillus coli communis) recovered fr gelatine and agar cultures. Streptococci very abundant
VII	2	3rd	BI	50 ccs.	Streptococci very abundant. Staphyllococci also present.
VIII	3	4th	BI	30 ccs.	Streptococci and Staphyllococci both recovered from gelatine and agar cultures. Staphylococci very abundant. Streptococci not present to any extent.
IX	$6\frac{10}{12}$	4th	BI	10 ccs.	Almost pure agar and gelatine culture of streptocpcci. Staphyllococcus pyogenes, aureus present, but few.
X	3	18th	BI	20 ccs.	Staphyllococci, diplococci, streptococci, and a short rod (probably B. Coli Communis) recovered from throat.

REMARKS

Well marked scarlet punctate rash. Both tonsils extensively ulcerated. Slight discharge from right nostril, only lasting for one day. Slight bilateral cervical adenopathy. No otorrhoea.

Typical punctate scarlatiniform rash universally distributed. Large excavated ulcer present over left tonsil. Profuse semi-purulent nasal discharge. Later the ulceration spread all over the throat and extended forward over the hard palate. Also involved the gums and the inside of the cheeks. Bright septic rash on the 9th day of illness over elbows and knees. Severe cervical adenopathy. Temperature half an hour before death 105.2° Fah. P.M. temperature 106.8° Fah.

Punctate scarlatiniform rash universally distributed. Both tonsils, anterior pillars of fauces, and uvula ulcerated: also soft tissues over hard palate, and inside of cheeks and gums. No nasal discharge. Moderate bilateral cervical adenopathy. Marked rigidity of lower extremities some days before death. Death on 62nd day of illness.

Considerable ulceration of the throat, Both anterior pillars of fauces are completely eaten through, and through the opening thus formed on the left pillar a large deep excavated ulcer is seen on the corresponding tonsil. The tongue is studded with a number of small excavated ulcers. Moderate bilateral cervical adenopathy. Left otorrhoea.

On admission diagnosis could not be confirmed. Nine days after admission a well marked punctate rash appeared over the trunk and extremities, with morning temperature 103.4° Fah. Ulceration over both tonsils and uvula. Profuse nasal discharge. On 7th day after appearance of rash a well marked septic rash noticed over dorsal surfaces of hands and feet. Aute-Mortem temperature 108.2° Fah. Death on 26th day of illness.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
XI	4	10th	BI	30 ccs.	Abundance of streptococci recovered from throat. In t aural discharge ba cillus tetragenus and diplococci als found
XII	5½	23rd	BI	20 ccs.	Streptococci and staphylococci present, the former abundant.
XIII	4	4th	BI	80 ccs.	Streptococci and st phylococci present the former very abundant.
XIV	4	9th	BI	65 ccs.	Streptococci and st phylococci present the former very abundant.
XV	8	13th	BI	40 ccs.	Streptococci and st phylococci present the former predomi ating.
XVI	4	6th	BI	60 ccs.	Staphylococci and Streptococci prese the former more numerous.
XVII	4	11th	BI	20 ccs.	Mixed infection wit Staphylococci and streptococci, the former predominat- ing.

REMARKS

Well marked rash over trunk and extremities. Both tonsils ulcerated, also anterior pillar of fauces and uvula. Discharge from both nostrils. Slight bilateral cervical adenopathy. Left otorrhoea.

A very sharp case of scarlet fever: rash patchy, almost morbilliform over thighs on outer and posterior aspects. Ulceration of soft palate and uvula began soon after admission and extended rapidly. Perforation through the soft palate on the left side. Severe bilateral cervical adenopathy. Double purulent otorrhoea.

Faint general punctate rash. Ulceration over both tonsils and anterior pillars of fauces. Nasal discharge sero-purulent in character. Very grave angina present with delirium and restlessness. Moderate cervical adenopathy.

General punctate rash well marked. Severe bilateral adenopathy. Ulceration over both tonsils and back of pharynx. No nasal discharge.

Rash general, punctate. Considerable ulceration over both tonsils. Slight cervical adenopathy. No nasal discharge. No otorrhoea.

On admission rash fading on legs and chest. Extensive ulceration of both tonsils, uvula and back wall of pharynx: sero-purulent discharge from nose, Severe diarrhoea all through illness: moderate bilateral cervical adenopathy. Death on 18th day of illness.

Case of very severe angina. Extreme ulceration of both tonsils and soft palate. Copious sero-purulent nasal discharge. Persistent diarrhoea all through illness. Lungs involved latterly. Moderate bilateral cervical adenopathy. Death on 12th day of illness.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
XVIII	4	7th	BI	160 ccs.	An almost pure staphylococci infection - a few streptococci present in the field.
XIX	3½	6th	BI	40 ccs.	Streptococci and staphylococci present, the former outgrowing the latter.
XX	3	6th	BI	20 ccs.	Streptococci and staphylococci both recovered from throat.
XXI	2	9th	BI	30 ccs.	Streptococci and staphylococci present, the former predominating.
XXII	3½	11th	BI	30 ccs.	Streptococci and staphylococci recovered from throat.
XXIII	6	7th	BI	40 ccs.	Streptococci and staphylococci, both recovered from throat.
XXIV	6	8th	BI	70 ccs.	Streptococci and staphylococci both recovered from throat, the former predominating.

REMARKS

Rash well developed, punctate, universally distributed. Extensive ulceration of both tonsils, especially right one. Profuse discharge from nose, sero-purulent in character. General enlargement of lymphatic glands in groins, axillae, and triangles of neck. Acute nephritis. Severe diarrhoea which persisted to the end. Death on 34th day of illness.

Rash well out on the face and simulates measles. On the body typically punctate in character. Extensive ulceration of both tonsils and soft palate. Nasal discharge abundant, sero-purulent in character. Moderate bilateral cervical adenopathy.

Rash has faded leaving injected red points on front of legs and on extensor surfaces of the arms. Profuse purulent nasal discharge. Diarrhoea severe and persistent. Ulceration over entire throat leading to perforation of the left velum palati. Double otorrhoea. Moderate cervical adenopathy on both sides.

A fading general scarlet rash, papular over external aspects of legs. Severe angina present. Profuse nasal discharge purulent in character. Ulceration over opposing surfaces of tonsils: also on gums and inside of cheeks. Moderate cervical adenopathy.

Rash typical and generally distributed. Throat structures extremely dirty looking, with deep ulcers on opposing surfaces of tonsils and over soft palate. Profuse sero-purulent nasal discharge. Inside of cheeks and gums involved in ulcerative process. Suppurative arthritis of right elbow joint. Double otorrhoea. Moderate cervical adenopathy.

Extensive ulceration on right tonsil, and on uvula. Profuse sero-purulent nasal discharge. Moderate cervical enlargement. Delirium present. Left otorrhoea.

Typical scarlet rash on trunk and extremities. Sloughy areas over both tonsils and soft palate. Sero-purulent nasal discharge. Moderate bilateral cervical adenopathy. Left otorrhoea.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
XXV	3	2nd	BI	30 ccs.	Staphyllococci and streptococci, the former very abundant.
XXVI	2½	10th	BI	20 ccs.	Streptococci and staphylloococci present, both abundant.
XXVII	3	10th	BI	80 ccs.	Streptococci and staphyllococci present, the former much more numerous.
XXVIII	3	12th	BI	60 ccs.	Mixed infection. Streptococci few in number. Staphyllococci very plentiful.
XXIX	5	7th	BI	70 ccs.	Mixed infection. Staphylloococi much more numerous than streptococci
XXX	1 5/12	4th	BI	20 ccs.	Streptococci and staphylococci present the former very plentiful.
		SERIES III. CASES CHARACTERISED BY EARLY AND PATCHY RASHES. EXTREME			
XXXI	3	12th	BI	40 ccs.	Streptococci and staphylococci present the former very abundant.

REMARKS

Rash well out and characteristic. Fauces, palate and tonsils much injected: the latter being ulcerated. Copious sero-purulent nasal discharge: moderate enlargement of submaxillary glands: death 3 days after admission on 4th day of illness.

Rash "went in" very quickly. Extensive faucitis and ulceration of both tonsils, uvula and soft palate. Foul-smelling nasal discharge. Severe angina present. Slight cervical adenopathy. Death on 11th day of illness.

Typical punctate rash. Severe ulceration over both tonsils and uvula. Gums, inside of cheeks and lips also involved in ulcerative process. Serous nasal discharge. Slight cervical adenopathy. Violent delirium present. Double otorrhoea. Inflammation of left eye: lachrymal abscess formed.

No rash present, but well marked desquamation. Extreme ulceration over both tonsils, uvula, anterior pillars of the fauces and posterior wall of pharynx: also implicates gums and inside of cheeks. Severe bilateral cervical adenopathy. No nasal discharge. Death on 16th day of illness.

Patchy punctate rash universally distributed. Tendency to assume papular form in parts. Great enlargement of cervical glands with brawny infiltration of the cellular tissue of the neck. No nasal discharge. No otorrhoea. Death on 12th day of illness.

No rash made out. Ulceration on left side of soft palate. Profuse nasal discharge, semi-purulent in character. Diarrhoea persistent. Moderate bilateral cervical adenopathy. No otorthoea.

ULCERATION OF THE THROAT, AND ATTENDED WITH LIVID

DEPRESSION A MARKED FEATURE

Rash universally distributed, somewhat papular over back. Markedly livid in colour. Extensive and deep ulceration of right tonsil. Moderate cervical adenopathy. Double otorrhoea very profuse. No nasal discharge.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
XXXII	6	9th	BI	70 ccs.	Streptococci and staphylococci both recovered from throat and from gelatine agar tubes: streptococci very abundant
XXXIII	2	6th	BI	100 ccs.	Staphylococci, diplococci, and streptococci recovered. Staphylococci outnumber other organisms.
XXXIV	2	6th	BI	20 ccs.	Practically a pure infection of staphylococcus pyogenes aureus. One chain is found in two or three coverglass preparations
XXXV	6	10th	BI	20 ccs.	Streptococci and staphylococci present the former very abundant.
XXXVI	4	9th	BI	30 ccs.	An almost pure infection of streptococci.
XXXVII	2½	8th	BI	60 ccs.	An almost pure infection of streptococci, associated with diplococci.
XXXVIII	4	4th	BI	20 ccs.	Staphylococci and streptococci recovered from throat.

REMARKS

Punctate, livid rash universally distributed. Extensive and deep ulceration over both tonsils and anterior pillars of fauces. Slight nasal discharge. Double otorrhoea. Severe cervical adenopathy.

Livid and patchy rash. Ulceration very extensive of both tonsils and uvula. Profuse semi-purulent nasal discharge. Extreme diarrhoea all through illness. Bronchopneumonia supervened before death. Moderate cervical adenopathy. Death on 17th day of illness. Ante Mortem Temperature 107.4° Fah.

Livid and patchy rash over extremities. On trunk it is bright scarlet and confluent. Ulceration over right tonsil and right anterior pillar of the fauces. Profuse nasal discharge. Very severe bilateral cervical adenopathy. Death on 9th day of illness.

Scarlatina anginosa of a very asthenic type. Rash patchy and livid over lower extremities. Deep ulceration over both tonsils. Profuse purulent nasal discharge. Moderate bilateral cervical adenopathy.

Rash punctate, patchy and livid over thighs. Extreme ulceration over both tonsils and soft palate. Copious sero-purulent discharge from nose. Moderate enlargement of the submaxillary glands. Death on 28th day of illness.

Rash livid over lower extremities, opposed surfaces of tonsils deeply ulcerated, no nasal discharge. Slight enlargement of submaxillary glands. Extensive broncho-pneumonia in right lung before death. Death on 28th day of illness.

Livid rash which ultimately became petechial in nature. Profuse muco-purulent discharge from nose. Severe diarrhoea from onset. Severe enlargement of submaxillary glands. Extreme angina. Death on 12th day of illness.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
XXXIX	6½	5th	BI	110 ccs.	Mixed infection. Staphylococci, streptococci and diplococci recovered from throat.
XL	3½	6th	BI	20 ccs.	A pure staphylococcic infection. No streptococci nor Loeffler's bacilli present.
XLI	7	11th	BI	20 ccs.	Mixed infection. Staphylococci, diplococci and streptococci recovered from cultures.
XLII	1 3/12	8th	BI	80 ccs.	Mixed infection. Staphylococci outnumbering Streptococci.
		SERIES NO. IV. CASES IN WHICH THERE WAS NO			ATTENDED WITH A PROFUSE
XLIII	1 10/12	6th	BI	10 ccs.	Streptococci and Staphylococcus pyogenes aureus both present. Practically a pure culture of streptococci recovered from nasal discharge.
XLIV	1 2/12	13th	BI	20 ccs.	Staphylococci, streptococci and diplococci recovered from throat. Streptococci very abundant.

REMARKS

Rash universally distributed, blotchy and livid over forearms. Hectic flush over cheeks: large necrotic patches over tonsils and soft palate. Profuse serous nasal discharge. Severe bilateral cervical adenopathy: double otorrhoea. Severe angina present, severe and persistent diarrhoea, death on 28th day of illness.

Rash over face is somewhat morbilliform. Severe cervical adenopathy, with infiltration of cellular tissue round about. Considerable purulent nasal discharge. Broncho-pneumonia before death. Death on 10th day of illness.

No rash observed, but well marked desquamation over hands and feet. Deep and extensive ulceration of throat structures. Profuse purulent nasal discharge: septic rash on extensor surfaces of elbows, knees, and over front of both ankles on 12th day of illness, moderate enlargement of submaxillary glands. Death on 20th day of illness.

Typical rash present. Considerable faucitis with ulceration over left tonsil. Moderate enlargement of submaxillary glands. Serous nasal discharge. Extreme angina present. Death on 29th day of illness.

MANIFEST ULCERATION OF THE THROAT, BUT WERE

NASAL DISCHARGE

Sparse eruption, somewhat livid and patchy over the trunk. Throat covered with exudation. Profuse sero-purulent nasal discharge. Double purulent otorrhoea. Diarrhoea to the extent of five motions per diem. Moderate enlargement of submaxillary glands.

Rash typical and generally distributed. Mouth and throat covered with a dirty exudation. Profuse sero-purulent nasal discharge. Diarrhoea to the extent of four motions per diem. Moderate glandular enlargement.

SERUM THERAPY

No.	Age in years or fraction of year	Day of illness when first injection made	Kind employed	Total quantity used	Bacteriological Examination
XLV	5	16th	BI	30 ccs.	Streptococci and staphylococci, the former very abundant.
XLVI	5½	3rd	BI	30 ccs.	Streptococci abundant. Staphylococci also present.
		THIS CASE WAS ADMITTED SUFFERING FROM A RASH APPEARED ON HER EIGHTH DAY OF ASSUMED A SEVERE CHARACTER.			
XLVII	5	20th	BI	150 ccs.	Streptococci very numerous in throat. Cover glass preparations were made directly and agar and gelatine tubes inoculated with the pus from cervical abscesses. Both streptococci and staphylococci were recovered, the latter being very abundant.

REMARKS

Bright scarlet rash: profuse nasal discharge sero-purulent in nature. Enlargement of glands at angles of jaw. Throat covered with dirty exudation. No ulceration observed.

Rash is bright, patchy and raised on the limbs, simulating measles. On the trunk it is more confluent. Respiration is characteristic of naso-pharyngeal obstruction. Well-marked semi-purulent nasal discharge. Moderate enlargement of glands at angles of jaw. Throat dirty, but no evidence of ulceration. Double otorrhoea.

MILD ATTACK OF SCARLET FEVER. A MEASLES

RESIDENCE IN HOSPITAL. THE CASE THEREAFTER

Patient developed measles on 8th day of residence in hospital. Bronchopneumonia supervened two days after appearance of rash. Extreme ulceration of right anterior pillar of the fauces, both tonsils and uvula. Severe cervical adenopathy which went on to suppuration. No nasal discharge. Death from general tuberculosis.

OUTLINE OF TREATMENT

The serum used was obtained from the British Institute of Public Health. It was kept in a cool place, and was rejected if it showed any sediment. It was injected subcutaneously, either into the loose cellular tissue of the abdomen, or between the scapulae. The skin was first thoroughly cleansed with turpentine and methylated spirit, and then laved with a 1 in 40 solution of carbolic acid. The quantity injected at any one time never exceeded 20 cubic centimetres.

Four cases received only 10 ccs: fourteen cases received 20 ccs.: nine cases received 30 ccs.: four cases 40 ccs.: one case 50 ccs.: four cases 60 ccs.: one case 65 ccs.: three cases 70 ccs.: three cases 80 ccs.: one case 100 ccs.: one case 110 ccs.: one case 150 ccs.: and one case 160 ccs. In four cases only a single injection was made: in the remainder, the condition seemed such as to warrant further injection. Simple measures were also taken to keep the mouth and nose as clean as possible. With this aim in view boroglyceride or a weak solution of perchloride of mercury was used to keep the mouth clean, while boracic or sulphurous acid was used

for the nose.

In addition to this, whisky and brandy were given according to the requirements of the case, while convalescence was established by a liberal use of iron and tonics.

BACTERIOLOGICAL EXAMINATION

In all the cases a bacteriological examination of the throat was made, and in all, streptococci were discovered, although in a varying degree. In all the cases, with the exception of two, there was a mixed infection. In thirty-four cases, cover glass preparations made directly from the secretion of the throat and subsequent streak and stab cultures, revealed the presence of streptococci and staphylococci. In eight cases three or more different micro-organisms were found: in three cases an almost pure culture of staphylococcus pyogenes aureus was obtained: and in two cases an almost pure culture of streptococcus was demonstrated. Cover glass preparations made from the three cases which subsequently, by means of culture, proved to be staphylococcic infections revealed one or two streptococci in the field. On the strength of this fact serum treatment was commenced. It was subsequently abandoned.

In six of the eight cases in which three or more organisms were found in the throat, streptococci, staphylococci and diplococci were demonstrated: in one streptococci, staphylococci, and a short rod like the bacillus Coli Communis: and in another streptococci, staphylococci, diplococci, and a similar rod-like organism.

INCIDENCE OF RASHES AFTER INJECTION OF SERUM

Nine of the forty-seven cases treated were attended with rashes of varying description, and indefinite as to their time of occurrence. In addition to these rashes, there occurred in a number of cases a slight erythematous blush around the site of injection.

As regards their time of eruption two appeared on the seventh day after the serum was injected: two on the eighth day: one on the tenth day: two on the eleventh day: one on the fourteenth day, and one on the fifteenth day.

In character these rashes varied from a punctate type resembling a scarlatinal eruption to a condition of the skin which suggested morbilli. A very common form was a simple erythema with periodic efflorescences of

"wheels." The rash was sometimes polymorphous. In one case an urticarial rash appeared on the eleventh day after the injection. On the following day it assumed the form of an erythema multiforme on the limbs, face and scalp. In twenty-four hours thereafter it assumed the characters of an erythema on the trunk. This did not have the defined character it had on the limbs. It was not so much raised above the surface of the skin, its borders were not so defined, and it lacked the crimson colour it had twenty-four hours previously.

In the simple urticarial rash, the "wheels" were generally set on congested bases. In one case, however, there were no congested bases, but a general blotchy rash with numerous "wheels" appeared on the seventh day. On the tenth day the "wheels" had entirely disappeared, and the rash which remained was of a measly type. In one case on the tenth day after injection a morbilliform rash appeared on chest, back and limbs. On the thirteenth day a deep coloured general erythema, not unlike a scarlet rash, appeared on the trunk. On the limbs it still remained measly looking.

As regards the duration of the rash, this varied from one to seven days. In one case a preliminary rash of "wheels," set on a measly base, lasted for three days. It

then quite disappeared for four days when it again showed itself in similar characters to the first rash.

In some cases there was a coincident rise of temperature: in others there was none. The evening temperature in one case rose to 105.2° Fahrenheit.

In attempting to find an explanation for these cutaneous disturbances, it is obvious that they might be caused by the injection of the serum "per se" independently of any adventitious element it might contain, or by these foreign elements. Frequently on the argument of "post hoc ergo propter hoc" various manifestations have been attributed to the serum.

Three hypotheses are possible (1) that these disturbances depend upon a special exciting action of the serum itself: (2) to a personal susceptibility of the patient, or (3) to a combination of these two conditions. As rashes of different characters are brought out in some individuals by the injection of normal serum, one is forced to the conclusion that this must be looked upon as a non-preventible accident of serum therapy, and will occur, in some measure at least, no matter with what care the serum is manufactured. There is no doubt, however, that, with an increase in the care of the preparation, together with an exalted "immunisation value" of the serum, so that

smaller quantities might be injected, these cutaneous disturbances will be reduced to a minimum. In the case where the evening temperature registered 105.2° Fah. the patient did not seem very ill, but had a high running pulse. The temperature and pulse rapidly subsided with the disappearance of the rash. In this case there was a somewhat excitable disposition of the patient which probably accounted for the thermal disturbance.

ABSCESS AT SITE OF INJECTION

In spite of every precaution taken to prevent this, three abscesses formed at the site of injection of the serum, and in other three cases a certain amount of oedema supervened in the cellular tissue round about. In no case was the well being of the patient interfered with.

INFLUENCE OF SERUM ON TEMPERATURE

The reduction of the temperature after injection of the serum has been insisted on by various observers, and considerable depressions accompanied by various critical

phenomena, such as profuse sweatings, lowered pulse and respiration have been noted. In the author's experience these views are not supported, but are on the whole contradicted. In twenty-one cases the temperature was taken half hourly for some time after the injection was made, and although in the first register or two a lower reading may have been recorded, this was never sustained for any length of time. In all the cases treated the temperature was taken either two hourly or four hourly through the whole course of the illness, and the results were very variable. In twenty-seven cases there was no appreciable effect on the course of the febrile movement: in fifteen cases the effect was variable, sometimes showing a rise, and at other times a fall: and in five cases the effect was such as to call for special comment. In none of the fifteen cases in which the effect was variable did the temperature ever show an upward or downward oscillation of more than 1° Fah.

Of the five cases which showed a marked result the first showed a rise of 1.6° Fah. an hour after the serum was given, which was maintained for some time. In the second case the temperature at 6 a.m. was 105° Fah., at 1 p.m. 100.8° Fah. The serum was injected at 1.45 p.m. The temperature registered at 3 p.m. 104.2° Fah., at 5

p.m. 104.2° Fah., and at 9 p.m. 103.4° Fah. In the third case there was a fall of 1.2° Fah. an hour after injection, which was not maintained: in the fourth case the temperature, fifteen minutes before the injection of the serum, registered 101° Fah., forty minutes after the injection was made it registered 104° Fah., and in the fifth case the temperature registered 104° Fah. at 9 p.m., serum was injected at 11.30 p.m. and the temperature at midnight registered 99.8° Fah. In the last case tepid sponging, which had been used to depress the temperature, was discontinued at 9 p.m. The temperature rose again to 103.6° in six hours. The pulse generally followed the temperature in all the cases: the respiration curve was very variable, and depended more or less on the condition of the lungs. These results have convinced the author that the serum is unreliable in its effects on the temperature curve.

INFLUENCE OF SERUM ON GLANDULAR INVASION AND SUPPURATION

Of the forty-seven cases under treatment, all had glandular affections to a more or less degree. In eight cases

the condition was one of "slight bilateral cervical adenopathy." In twenty-eight cases the condition was one of "moderate bilateral cervical adenopathy;" in nine cases of "severe bilateral cervical adenopathy," and in two cases of "very severe bilateral cervical adenopathy." In none of the cases had surgical measures to be resorted to. The application of cold compresses was alone sufficient.

Of the two cases of very severe adenopathy, fluctuation was made out in one on the morning of the death of the patient. This was Case No. XXXIV, and was almost a pure staphyllococcic infection. In the other case (No. XXIX) no fluctuation could be made out, but considerable oedema and brawny induration of the neck. In this case the submaxillary glands on both sides were much infiltrated, accompanied by well marked oedema of the face. The cellular tissue in the middle line of the neck was markedly oedematous, and this condition extended down as far as the level of the second rib. Under serum this condition greatly improved. Both the oedema and the induration almost entirely disappeared, and the infiltrated glands at the angles of the jaws could be distinctly delimited. No fluctuation could be made out. Infection was a mixed one, the staphylococci predominating.

Of the nine cases of severe adenopathy only one suppurated, and this case presented special features. This patient was admitted suffering from a mild attack of scarlet fever. On the eighth day after admission she developed measles, and was transferred to a ward under the charge of a colleague. Under the agency of both the scarlatina and measles virus, the throat condition became much worse, ultimately resulting in a severe ulceration. With this condition a marked cervical glandular enlargement developed, for which poultices were applied. An abscess formed and pointed, and the pus was evacuated spontaneously. A drainage tube was inserted and the abscess cavity healed up. The pus formation in this case could scarcely be accounted for by the scarlatinal virus alone, as prior to the invasion of the measles the case was a mild infection. Cover glass preparations made from the pus in this case showed an abundance of staphylococci with a few streptococci.

Of the twenty eight cases of "moderate cervical adenopathy," and eight of "slight cervical adenopathy," none suppurated, although attended in several instances with extreme ulceration of the throat. In only one case, therefore, did suppuration occur at any stage of the illness. Bacteriological examination revealed in this case

an almost pure staphyllococcic infection.

This is an important fact when it is remembered that glandular infection and abscess formation is a common condition among children who suffer from scarlatina anginosa, more especially in the debilitated and strumous type of children treated in a large public institution.

INFLUENCE OF SERUM ON NASAL DISCHARGE

In a large number of cases of scarlatina anginosa, a nasal discharge is one of the earliest symptoms. The infaammatory process does not confine itself to the tonsils, anterior and posterior pillars of the fauces, uvula and pharynx, but also extends to the naso-pharynx. There is good reason to believe that a nasal discharge is due to some ulcerative process in this region, or in the upper part of the nasal mucous membrane. The factor which determines the locale of the commencing ulceration in scarlatina anginosa will always be doubtful, but, in cases where a nasal discharge is one of the earliest symptoms in the disease, a swab from the naso-pharynx or an agar or gelatine tube sown from a

nasal discharge, after the nose has been thoroughly syringed with a weak antiseptic, almost invariably yields a pure culture of streptococci. The longer the delay in making a culture, there is a less probability of a single organism being found. When an early nasal discharge is treated promptly with antistreptococcus serum, there is, in many cases, a considerable diminution, and in some a complete arresting of the discharge. The actual result is, in the author's opinion, to be measured as the serum is exhibited early or late in the disease. The effect of the serum given early in the disease where there is copious nasal discharge is, in his opinion, a decidedly beneficial one. If the treatment is delayed till the staphylococci outnumber other organisms in the cultures, the serum is useless in affecting the discharge.

The effect of the serum was shown particularly in the following four cases which bear out the above remarks.

L. S. aet. $1\frac{10}{12}$ years. Admitted on fifth day of illness with sparse eruption, patchy and livid over the extremities. Throat covered with exudation. On removing this from the anterior pillars of the fauces and tonsils deep ulcers are observed. Profuse sero-purulent discharge from both nostrils. Purulent discharge from

both ears. Diarrhoea to the extent of five motions in the twenty-four hours. Moderate cervical adenopathy. Ten ccs. serum injected morning after admission. The following day a considerable diminution of the nasal discharge had taken place, and its character was now a glairy mucous one. In another twenty-four hours the discharge had quite ceased.

Bacteriological Examination: Streptococci and staphylococci present, the former very abundant. An almost pure culture of streptococci obtained from nasal discharge.

W. D. aet. 5½ years. Admitted third day of illness with a patchy scarlet rash. Profuse semi-purulent nasal discharge. Moderate enlargement of glands at angle of jaw. Throat very dirty. Double otorrhoea. Nasal discharge ceased four days after admission. Had in all 30 ccs. of serum.

Bacteriological Examination: Streptococci and staphylococci both recovered from throat. Streptococci very abundant in nasal discharge.

E. B. aet. 2 years. Admitted third day of illness. Profuse semi-purulent nasal discharge from both nostrils. Received 30 ccs. of serum in all. Discharge

entirely ceased twenty four hours after injection of first 10 ccs. On the following day a slight re-establishment of the discharge took place, serous in nature. This ceased finally five days after.

Bacteriological Examination: Streptococci very abundant. Staphylococci also present.

J. C. aet. 9 years: Admitted 6th day of illness. Profuse sero-purulent nasal discharge. Serum injected 10 ccs. Nasal discharge ceased forty eight hours after injection.

Bacteriological Examination: Streptococci and staphylococci present. Streptococci extremely abundant in nasal discharge.

INFLUENCE OF SERUM ON ULCERATIVE CONDITIONS OF THROAT

The beneficial effects which followed the use of the serum in some cases which showed extreme ulceration of the throat cannot, in the author's opinion, be disputed. Within twenty-four hours after injection the effect was in some cases very marked. In cases which showed a pseudo-membrane over both tonsils, there was often a

successful exfoliation of the membrane leaving a raw sore underneath which, with the continued application of the serum, showed all the characters of a healthy granulating ulcer. In other cases where no pseudo-membrane was present, but were characterised by deep unhealthy looking ulcers, under serum these either spontaneously became much cleaner, or nurse reported that the throat could be cleaned much more easily by the local measures used. In other cases where the serum was administered before ulceration commenced, it was observed that a sharp line of demarcation began to form at the outer edge of the necrotic patch, the exfoliation of which seemed to be hastened, leaving a healthy looking ulcer underneath.

In some cases the local condition improved much more rapidly than the improvement in the general condition seemed to warrant, while in other cases a local improvement took place with no apparent change in the constitutional state.

In other cases, on the contrary, which seemed to be comparable in all respects, both from the bacteriological and clinical standpoint to those quoted above, no improvement, either local or constitutional, took place. The author has considerable difficulty in ex-

plaining these results. The treatment was commenced as early and pushed to the same extent as in the other class of cases. Moreover in two cases, where bacteriological examination revealed an almost pure streptococcic infection, and in which the treatment was pursued vigorously no improvement took place, and both patients went rapidly downhill. It is a well known fact that when two organisms live symbiotically, the action of one is often enhanced by the mere presence of the other, and in many cases in a direct ratio to the preponderance of one over the other microbe. This theory may explain the varying results obtained in the cases of mixed infection treated in the series, but it does not throw any light on the unsuccessful issue of the two cases above mentioned where the infection was practically a pure streptococcic one.

INFLUENCE OF SERUM ON ALBUMINURIA

The incidence of albuminuria in scarlet fever is not confined to the anginous type, and is as commonly associated with very mild attacks of fever as with the more severe forms. This consideration makes it impossible

to deduce much as regards the action of the serum in preventing or mitigating renal affections.

In three cases of those treated in the series nephritis supervened. In one case albumen to the extent of 1/2 with blood appeared in the urine on the twenty-seventh day of illness, and was associated with general anasarca. In another case a deposit of albumen with blood and associated with oedema of the legs and feet appeared on the twenty-fifth day of illness. In the third case a large quantity of blood, albumen, and organic debris appeared in the urine on the eighteenth day of illness.

Generally speaking, the third week of illness is the incidence period of renal affections in scarlet fever, so that these instances follow the usual rule.

INFLUENCE OF SERUM ON OTORRHOEA

It is well nigh impossible to draw conclusions from anything that happens in ear discharges. These are known to be subject to considerable variations when no treatment is exhibited. The thorough cleansing of the ear also with some simple antiseptic has often a good in-

fluence either in arresting or lessening ear discharge, so that any value attached to the serum in influencing the flow is easily criticised.

TABLE OF MORTALITY OF CASES

Bronchopneumonia	5
Bronchopneumonia and severe diarrhoea	2
Extreme toxic infection	7
Uraemia with convulsions	2
Uraemia with diarrhoea	1
Extreme toxic infection and diarrhoea	1
Extreme diarrhoea with exhaustion	2
Diphtheria (post scarlatinal)	1
Heart Failure	2
Tubercular laryngitis and general tuberculosis	1
	24

The deaths attributed to diphtheria, heart failure and tuberculosis could scarcely be due to inefficiency of the serum. In the case which succumbed to post scarlatinal diphtheria the use of the serum was attended with the best results in arresting a very destructive and quickly spreading ulcerative process in the throat. The patient had a long convalescence. Fourteen days after she was allowed up, diphtheritic membrane appeared over both tonsils. Three days afterwards the patient

became asphyxiated. Tracheotomy was performed, but patient died two hours after the operation.

The two deaths due to heart failure occurred when both patients seemed quite out of danger so far as the toxic infection was concerned. The death from tubercular laryngitis and general tuberculosis occurred in a case mentioned previously. The patient was suffering from scarlatina on admission and developed a morbilliform rash, with choriza and lacrimation, on the eighth day of residence in hospital. Bronchopneumonia set in and apparently afforded a nidus for the tubercle bacillus.

If these four cases be deducted, the mortality is 20 or 42.5% of the cases treated.

The following abridged notes of four cases are taken from the Ward Journals. They are illustrative of four distinct types of the cases treated, either from the point of view of local lesion or general characters:-

CASE I. ILLUSTRATIVE OF SEVERE IMPLICATION OF THROAT.

M. B. 6 10/12 years. Admitted 1st April 1898. Illness began last night with headache and sore throat. Vomited once. Rash seen today on trunk and limbs. Has had measles and whooping cough.

2nd April: Throat is looking extremely dirty and a foul excavated ulcer is present on the anterior pillar of the fauces on the left side. The right tonsil is raw and ulcerated towards the middle line of the mouth.

3rd April: The throat this morning very dirty, and there is considerable superficial necrosis of the soft tissues on the roof of the mouth.

4th April: The throat is still looking dirty, and the ulcer on the left anterior pillar of the fauces is certainly extending. The back wall

of the pharynx is superficially necrosed. 10 ccs. serum injected today.

5th April: Throat is looking somewhat cleaner this morning.

7th April: Ulcer on left anterior pillar of fauces is looking much healthier and appears to be smaller today. A demarcating zone is observed today for the first time.

8th April: Throat is greatly improving.

10th April: Improvement continues and all the ulcers including those over the tongue are healthy looking.

13th April: Granulations observed today over soft palate and posterior pharyngeal wall.

15th May: Patient allowed up today. An examination of the throat shows considerable deformity. The anterior pillars of the fauces are drawn apart exposing the two tonsils of unequal size, the right being smaller than the left one as the result of its involvment in the ulcerative process. A very small shred of the uvula is left. The soft tissues over the hard palate are puckered and glazy looking.

CASE II. ILLUSTRATIVE OF GENERAL SEPTIC ABSORPTION.

J. T. aet. 3½ years. Admitted 3rd October 1896. Illness began three days ago with sore throat, diarrhoea, and slight cough. Rash seen second day. No other infectious disease.

5.30 p.m. Tongue strawberry. Temp. 104.4, pulse 140, Resp. 42. Rash fading on limbs, but well marked on trunk. Throat congested. Considerable exudation on both tonsils.

4th October: Throat very dirty, especially on right side. Slight nasal discharge.

5th October: Fairly quiet night. Less exudation on fauces.

6th October: Superficial ulceration of the fauces, but little swelling.

7th October: Small ulcer on uvula. Sloughy condition of left tonsil.

10th October: There is a large sized slough on left side of the soft palate today, and a similar necrotic area on the right side, but not so extensive. There are also one or two small ulcers on the uvula.

11th October: 10 ccs. serum injected today.

15th October: Condition of throat is improved. Ulcers looking healthier.

17th October: Complains of pain at right elbow, especially on movement. There is some swelling around the joint. No redness. Tongue dry and glazed.

18th October: Throat is still improving.

20th October: Temperature is still elevated. Locally the throat is much improved. Elbow is very painful. There is still considerable swelling round the joint, and the forearm is held midway between pronation and supination. Movement causes pain.

22nd October: Improvement in throat condition maintained. Temperature lower, pulse better in quality: slough in throat is detaching itself leaving a red healing surface exposed.

28th October: This afternoon the elbow joint appears to be much more swollen, is very tender on pressure and decidedly fluctuant. An exploring needle brought out a quantity of healthy looking pus.

29th October: Today under chloroform made an incision on outer and posterior aspect of elbow, and evacuated several ounces of pus. Enlarged in-

cision and explored with finger, and found elbow joint opened with sinuses passing up the arm towards the shoulder and round the posterior aspect of the humerus. No eroded bone found either in the joint or outside it. Drainage tube inserted. Soft palate cicatrising.

2nd November: A little pus exudes from the joint. Throat now perfectly healed.

3rd November: Arm put up in a fixed position today.

20th November: Sinuses practically healed. Cannot move the arm herself, and painful on passive movement.

7th January 1897: Patient dismissed today. The arm could be moved to a certain extent. In raising it she had to support it by the left arm.

Patient received in all 30 ccs. of serum.

CASE III. ILLUSTRATIVE OF A QUICKLY SPREADING BRONCHO-PNEUMONIA, PROBABLY CAUSED BY INSUFFLATION INTO THE TRACHEA OF SMALL NECROTIC AREAS.

E. B. aet. 2 years. Admitted on second day of illness with sickness, vomiting, and sore throat. Rash seen today.

Throat is congested and extremely foul looking over both tonsils. Slight nasal discharge.

30th March: Fairly profuse nasal discharge from both nostrils, semi-purulent in character. The throat looks dirty behind, and on the left tonsil there is a deep excavated ulcer. This is the only loss of tissue that can be observed. 10 ccs. of serum injected today.

31st March: Nasal discharge has ceased today from both nostrils. Throat is looking much cleaner, and the ulcer on the left tonsil is certainly not extending.

1st April: Slight re-establishment of nasal discharge. 10 ccs. serum injected.

3rd April: Tissues over hard palate are necrotic. 10 ccs. serum.

7th April: Throat is not looking so favourable. The ulcer over the left tonsil is extending and also the area of necrosis over the hard palate. 10 ccs. serum.

8th April: General condition very unfavourable. A bright septic rash has appeared today over the elbows and ankles extending on the right leg up to the knee.

10th April: Patient is still very ill. Is taking her milk and stimulant well. Bronchopneumonia

has developed. Both lungs affected generally.

11th April: Patient passed a restless night. The throat is looking somewhat cleaner. Respirations this morning number 76. Condition is very unfavourable.

13th April: Patient died at 5.15 this morning. Slight nervous twitchings and subsultus before death. At five o'clock the respirations reached 100. Patient received in all 50 ccs. serum.

CASE IV. ILLUSTRATIVE OF EXHAUSTION FROM EXTREME DIARRHOEA AND ATTENDED WITH A FATAL ISSUE.

M. D. aet. 6½ years. Admitted on second day of illness with sore throat, sickness, and diarrhoea. Temp. 102.8, Pulse 144, Resp. 40.

19th September: Very restless last night. Rash generally distributed, especially well marked over arms where it is somewhat patchy. Face pale with blotchy, hectic flush on cheeks. Patient heavy and ill-looking. Profuse watery discharge from nose. Pulse rapid and very shabby. Fauces, palate and tonsils are extremely angry looking, and both tonsils are covered with a purulent exudation. On the

opposing surfaces of both tonsils and on the uvula and anterior pillars of the fauces there are grey necrotic patches.

22nd September: No change in local condition. Child is very restless. Three motions during the night. Nasal discharge as profuse. General condition is still extremely grave. Pulse suggests a failing ventricle contracting spasmodically and incompletely. 10 ccs. serum injected.

24th September: Pulse is distinctly better in quality today, less jerky and more sustained. The throat is improved, and here and there are indications of granulations.

26th September: A very decided improvement has taken place in condition of patient. The septic process in the throat is now quite localised, and the sloughs are separating. Nasal discharge has almost ceased.

28th September: Improvement in throat condition is maintained. The sloughs have completely separated, and healthy ulcers are seen over anterior pillars of fauces and tonsils.

2nd October: Patient has gone back since last note.

Temperature and pulse have again risen. Pulse of spasmodic type it had at previous stage of illness. Diarrhoea began three days ago: four to five motions in the twenty four hours.

3rd October: Passed a very restless night. Throat is still looking well and the destructive process has ceased.

5th October: Diarrhoea still continues: four to five motions in the twenty-four hours.

The diarrhoea continued till the afternoon of the 14th October when patient died suddenly. In the morning she was looking brighter. Throat was quite healed.

REMARKS ON THE TREATMENT WITH A CONSIDERATION OF RESULTS

The cases treated were patients in Belvidere Fever Hospital during the years of 1896, 1897 and 1898, during which time the author was a Resident Assistant Physician.

As a premise it should be stated that the serum was put to a severe test as all the cases were marked examples of the anginous type of scarlet fever. This was purposely

done in order to determine the exact place antistreptococcus serum should hold in the therapeutics of this affection. In assigning the proper value to a new remedy, unless its use is founded purely on an empiric basis, it is essential that it be exhibited upon rational and scientific lines. Especially is this the case with the application of sera to human disease. These are the fruit of work done for years along particular lines of study, and they cannot justifiably be administered to any case in a haphazard fashion. A bacteriological examination therefore should always be made. Anti-streptococcous serum is directed against the ravages of the streptococcous on the human economy, and it is useless to expect good results from its employment in conditions where other micro-organisms predominate. The author would therefore put in a plea for exactitude in the use of sera. In the use also of antistreptococcous serum in cases of streptococcal invasion of surfaces exposed to the air, good results can scarcely be expected to take place if the treatment be delayed, as a primary simple infection is very soon converted into a mixed one. If the doctrine of the unity of the streptococcal germ, so far as toxine formation is concerned, be upheld, the formation of a powerful antitoxin would naturally be the best means

of counteracting the ravages of any streptococcal affection. The difficulty of praparing a potent filtered toxine has been stated previously. Failing in their attempts in this direction, laboratory investigators set about making a bactericidal serum. It has been shown how a serum prepared from a specific streptococcus will only protect animals, in a restricted sense, either against the corresponding organism or one closely allied to it. Further, it has been proved that in proportion to the number of different races of streptococci injected into a horse, is the antimicrobic power of the resulting serum measured.

In the light of these facts, there is a strong argument, in the author's opinion, in favour of the preparation of "polyvalent" sera. During last year at the British Institute of Preventive Medicine Farm at Sudbury, streptococci from two sources have been used; (1) from an acute abscess, and (2) from a fatal case of acute septicaemia. No. 1 after its virulence is exalted by the passage method through rabbits is so powerful that one millionth of a cubic centimetre of liquid culture kills a rabbit in twenty-four hours.

If a bactericidal serum has to be used, one of even a more compound nature might with advantage be prepared.

Van de Velde suggested that as the agglutinating action of a serum on a particular race of streptococcus is in direct proportion to its bactericidal property, cultures of streptococci from various sources should be tested against the blood of the patient. These streptococci could have their corresponding sera prepared. The serum which corresponded to the organism which agglutinated in the shortest time, by the action of the patient's blood, would be the one most likely to stem the progress of the disease.

There is no doubt, however, that a "polyvalent" serum is superior to this method of treatment. In the course of a streptococcal infection, some time must elapse before the different bactericidal substances are formed in the blood which exert an agglutinating action on the particular race of streptococcus concerned, and the longer treatment is delayed the less likely is a favourable termination.

It has also been clearly shown that there is good reason for the belief that the strength of an antistreptococcus serum is extremely liable to diminish if it be kept for any length of time. In the sera first prepared, a little phenol was added to preserve them. This might account for the diminution in these cases.

There is now no antiseptic added, and any impairment of the strength of a serum must be due to the effect of physical or chemical agencies on an unstable compound. An interesting fact in regard to this was shown by the different behaviour of Marmorek's serum in the hands of different observers. The good results from this serum were all obtained by workers in France. It seems probable that these were able to obtain fresher supplies of the serum than those beyond its borders. The impairment of the strength of the serum is also demonstrated in the results of observers who used two sera, one prepared by themselves and the other obtained from another source.

In most instances positive results were obtained by their own sera, and unsatisfactory or negative results by the other serum. Their own sera were probably prepared more recently than the other.

The author has endeavoured to prove that although the efficacy of the antistreptococcus serum in certain cases is very marked, yet its applicability is of a limited nature. The lines have also been suggested along which a serum might be prepared which would be more comprehensive in its action. The good results which follow its use are mainly seen in its effects on

the local condition of the throat, in nasal discharges at an early stage of the illness, and on the glandular system. The invasion of the glandular system by an inflammatory process does not seem to be affected by the serum, as, in some cases, glandular enlargement took place after the serum was exhibited, and in other cases where glandular infiltration was present, this became even more marked after the serum was used. There is considerable reason in believing, however, that the serum exhibits an inhibitory influence on the process of suppuration, as in no case of the series in which streptococci predominated did pus formation take place, although in many cases the inflammatory process was very acute. The change in the condition of the throat was often more marked and showed itself more quickly than an improvement in the general condition. This would seem to indicate the necessity for an antitoxic rather than a bactericidal serum. The throat is the manufacturing place of the streptococcus toxine. This appears to be a very diffusible poison, and although the streptococci in the throat are presumably rendered harmless by the local action of the serum, the general circulation has received from the lymphatics of that region a sufficient dose of the toxine to lead to great depression. This toxine in

the circulation is of course not affected by the serum. In many cases the extreme depression lasted till the throat exhibited healthy granulating ulcers. The effect of the serum on the temperature must be described as unreliable. It is impossible to attribute any effect of the serum, either on the onset or the course of albuminuria occurring in this affection, as nephritis does not seem to be a commoner accident in the course of a severe attack of scarlet fever than of a mild attack.

The author would, therefore, submit, that as in the various complications of scarlet fever, there may be a plurality of races of streptococci concerned, or a different race of streptococcus connected with each case, a "polyvalent" serum has much to recommend it.

The want of success which attended some of the cases of the series might be due (1) to the serum used not being directed against the particular type or types of streptococci concerned, or (2) an impairment of the strength of the serum from some cause. There is no doubt that in the treatment of septicaemic conditions, the hope of the future lies in the discovery of a streptococcus antitoxin. The most potent antimicrobic serum yet prepared does not approximate to the power of the antidiphtheritic serum, against the toxin of the bacillus diphtheriae. At pre-

sent we must rely on a "polyvalent" bactericidal serum. The efforts of laboratory workers must be in the direction of preparing a more powerful and stable serum. The serum being then of a higher bactericidal value, the quantity necessary to be injected might be lessened. It has been found by preparing anti-diphtheritic serum of higher "immunisation value," and thereby lessening the quantity injected, that the cutaneous disturbances incidental to its use have been less frequent. Similar good results might follow an increase in the potency of anti-streptococcus serum.

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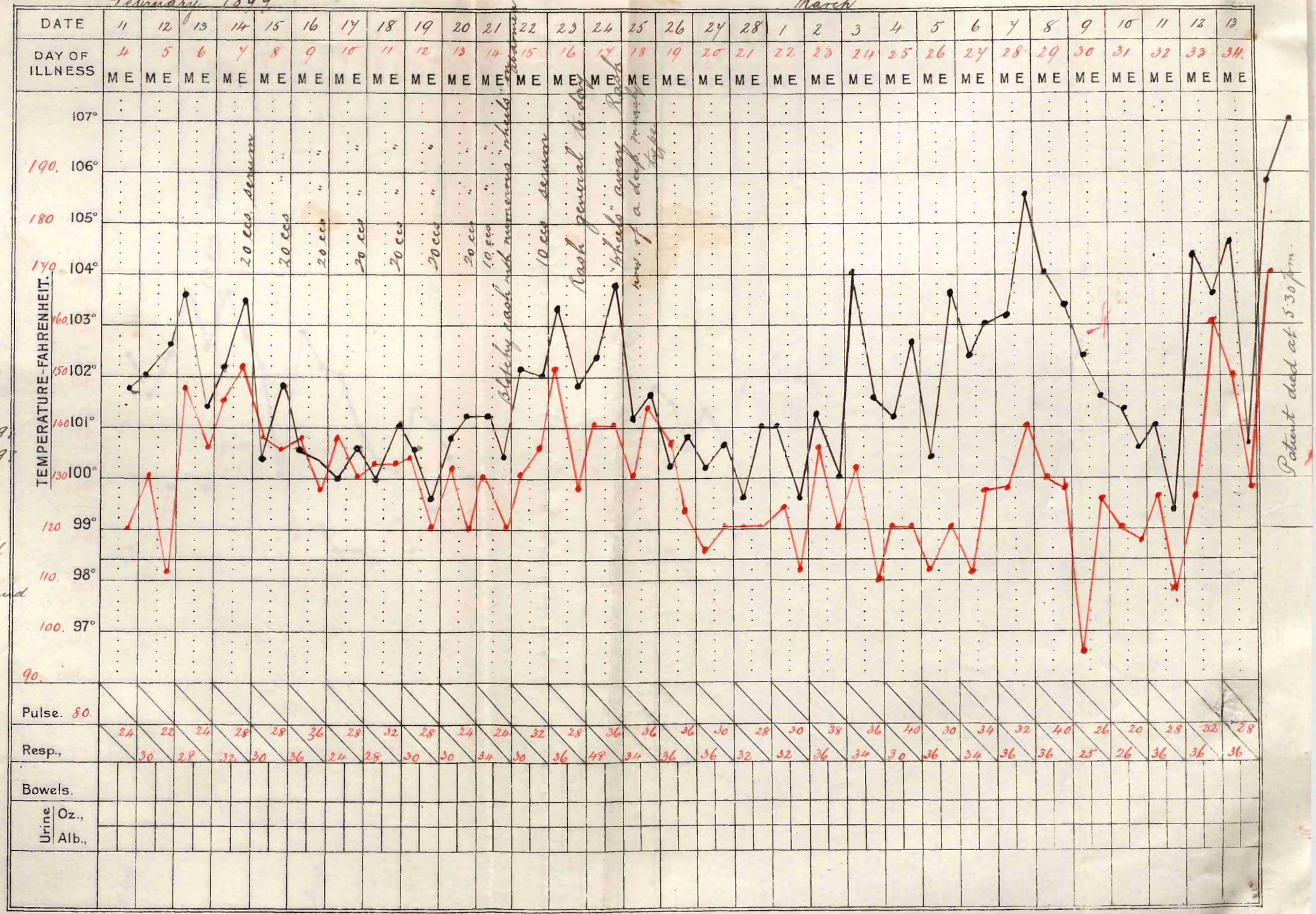
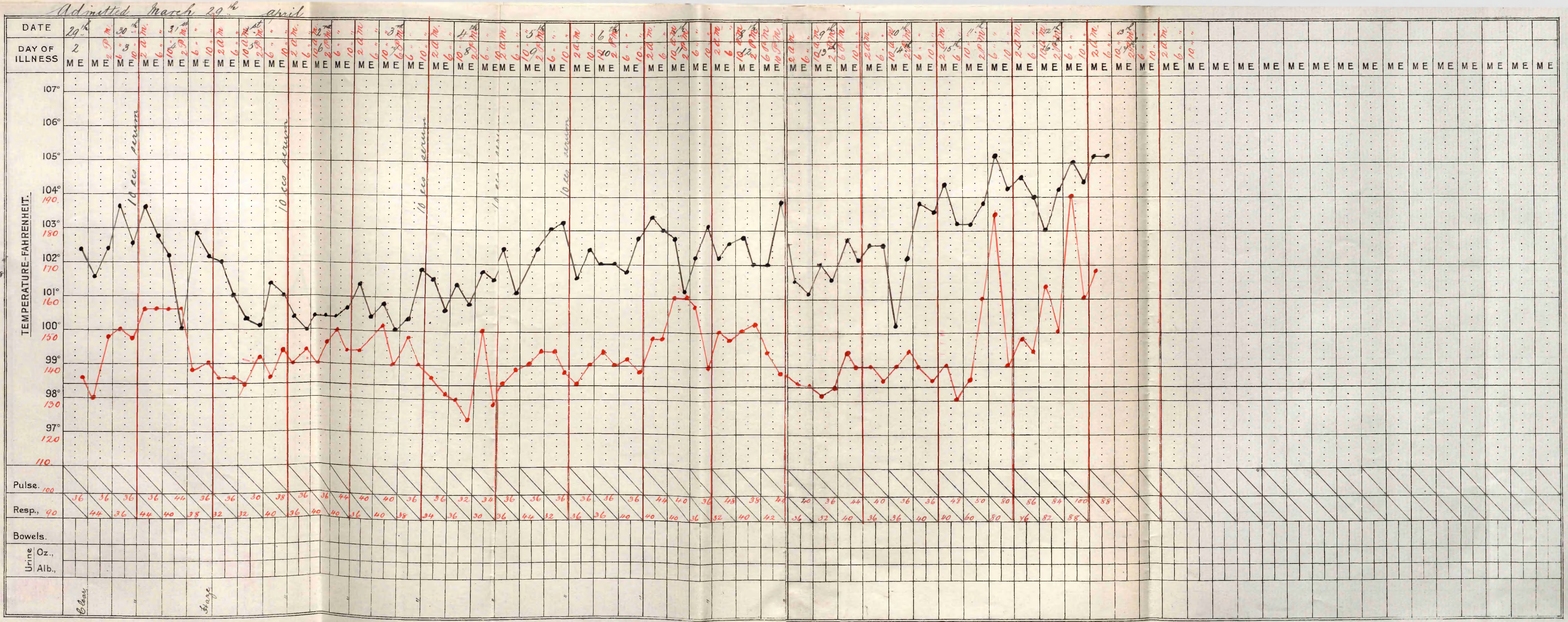


H. L. Art 4 years
Admitted 11th Febry 1894
Died 14th Mar. 1894

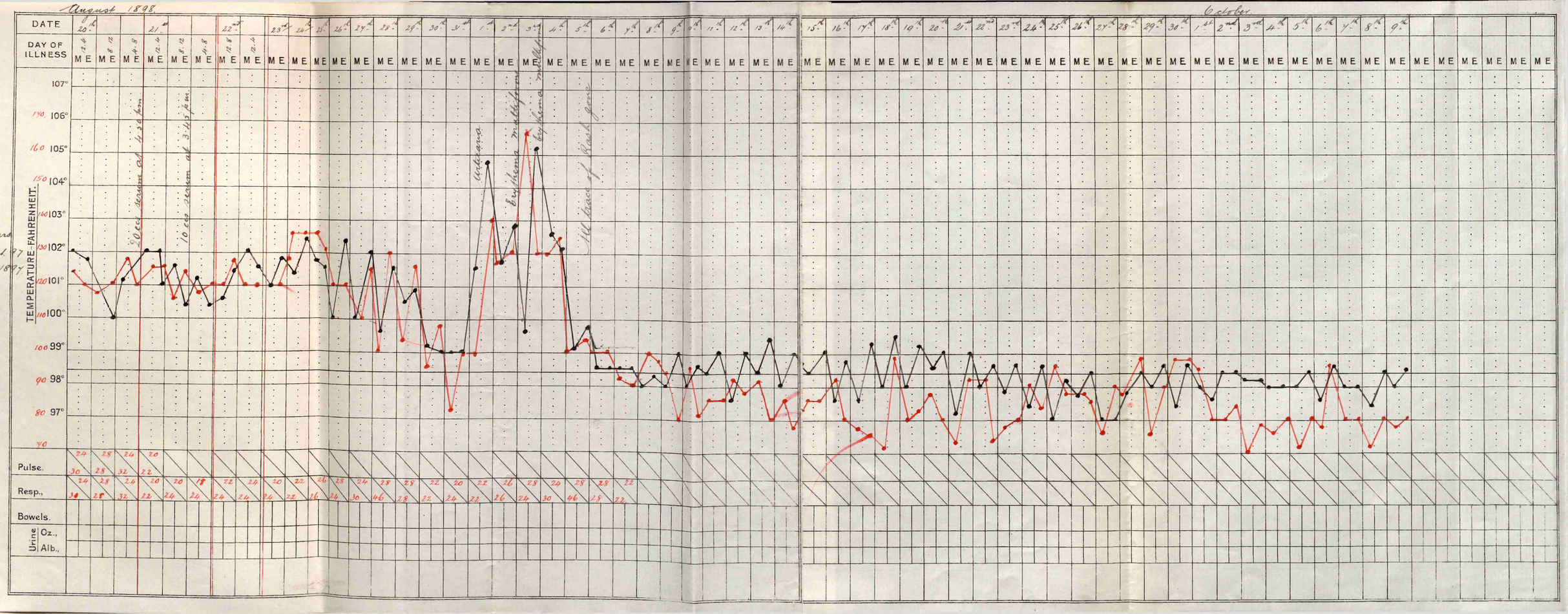
Chart showing disturbance of temperature caused by serum Rash. Death from profound toxaemia

B. Art. 2 years
mitted March 29th 1898
d 13th April 98
nchopneumonia
ving elevated
perature, pulse
& Respiration.



H. B. Art 6 years
[Ad]mitted 1st April 1898.

[Pa]tient developed scarlatinal [diph]theria during [con]valescence and [di]ed on 11th June [...] hours after [tra]cheotomy was [per]formed.



D. Art 5½ years
mitted 20th Augt 97
mised 13th Oct. 1897

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