THESIS FOR THE DEGREE OF M.D.
on
THE SKIN IN DIPHTHERIA:
A STUDY OF THREE HUNDRED AND EIGHTY CASES.

by

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In the following paper the cutaneous phenomena observed in three hundred and eighty cases of diphtheria are discussed.

The cases were collected during a period of sixteen months of residence in the Edinburgh City Hospital and the Leith Hospital for Infectious Diseases.
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Primary Diphtheria Rashes.

Before discussing those rashes which occur in Diphtheria from what may be called Secondary Causes—such as enema rashes, antitoxin rashes, etc., it is only logical to consider whether Primary Diphtheria Rashes do not occur; rashes part of the original symptom—complex of the disease, and not capable of association so far as can be ascertained with any secondary cause.

At the present time, when the great cause of secondary rashes—antitoxin—is in operation in every diagnosed case, the study of such a question is attended with considerable difficulty. It happens only too frequently, that, once diphtheria has been diagnosed and antitoxin given, every eruption occurring subsequently is labelled promiscuously "antitoxin rash": a piece of post hoc reasoning which is not only misleading, and unfair to antitoxin, but often productive of serious consequences. In view of this it is interesting to examine the history of the disease as it occurred in this and other countries before the introduction of antitoxin. We shall find that while the earlier accounts of the disease—prior to 1821—are often too indefinite to be of much value, its history subsequent/
subsequent to this date affords conclusive evidence of the occurrence of true-Diphtheria Rashes.

Historical Enquiry.

(a) Early times to 1821. Putting aside the descriptions of such early writers as Aretaeus and even Hippocrates as being doubtfully applicable to diphtheria, there is good proof that the disease was prevalent in Italy, Spain and other European countries in the sixteenth and seventeenth centuries. Accurate descriptions have reached us from Spain of the early seventeenth century in the writings of Herrera, Villa Real, and Fontecha - cases of morbus suffocans or "garrotillo" as it was graphically termed being recorded as early as 1580. Later, undoubted outbreaks in Sicily are described, less vividly, by Cortesius and Alaymus.

Coming to the history of the disease in this country, we find it in the eighteenth century under a variety of names - morbus strangulatorius, epidemic croup, malignant sore throat etc. An inspection of the records of epidemics of this period serve in the main to show us that while the identity of diphtheria is often undoubted its purity is not beyond question. We are constantly reminded not only of the confusion that existed between/
between diphtheria and scarlet fever (thus Withering, writing in 1793, contends that Scarlatina anginosae and "angina gangrenosa" are one and the same disease, arising from one specific infection) but also of the frequency with which epidemics of diphtheria occur alongside of outbreaks of scarlet fever and measles, or following closely on such outbreaks.

To quote an interesting case:—Dr. Fothergill, writing in 1748, described as "morbus strangulatorius" a disease which he contended was distinct from scarlet fever. The leading symptom was an infection of the throat - a diffuse redness with sometimes "a broad spot or patch of an irregular figure, and of a pale white colour, surrounded by a florid red." Later these white areas became ashy, and it was seen that "what at first might have been taken for the superficial covering of a suppurated tumour, was really a slough covering an ulcer of the same dimensions."

Now this description is in many ways suggestive of the essentially diphtheritic lesion. But Fothergill goes on to describe a rash: "Generally on the second day of the disease the face, neck, breast, and hands to the fingers' ends, are become of a deep erysipelas colour with a sensible tumefaction/
tumefaction: the fingers are frequently tinged in so remarkable a manner that, from seeing them only, it has not been difficult to guess at the disease. A great number of small pimples, of a colour distinguishably more intense than that which surrounds them, appear on the arms and other parts. They are larger and more prominent in those subjects, and in those parts of the same subject, where the redness is least intense, which is generally on the arms, breast, and lower extremities."

The rash here described is as realistically scarlatinal as the throat symptoms were definitely diphtheritic. The probability is that his epidemic consisted at first of cases of diphtheria + scarlet fever, and later of pure diphtheria: for he states that the eruption was not present in every case, and that in the later months of 1754 it was entirely absent.

This haziness and lack of definition is evidenced in reports of subsequent epidemics throughout the century, described by Nathaniel Cotton, Huxham, Wall: and make it almost hopeless to try to assign significance to the rashes recorded. Many factors tended to make difficult the separation of diphtheria from the essentially eruptive infections and especially from Scarlet Fever/
Fever;—the intermingling of epidemics: the tendency for a simple Scarlet Fever to take on diphtheritic characters: the occurrence of severe scarlatinás with great prostration and suppressed rash: and on the other hand the occurrence of mild cases due to reinfection in individuals who have had a previous attack, where throat symptoms alone are present.

Standing out in the midst of this confusion there are however notable records of what we must regard as pure diphtheria. As early as 1750 Starr describes such an epidemic occurring in Cornwall. A case of his, interesting as wound diphtheria, and described with a vividness foreign to modern scientific terminology, is worthy of reference. The lesion occurred on the raw surfaces left after blistering. "The blisters had been dressed with Colewort leaves, and ran but little; but, contiguous to them, small red pustules, not exceedingly fiery, arose, which, sweating plentifully, in a few hours became quite white. These, hourly enlarging their bases, united and covered a large surface, fresh pustules arising in the adjacent parts. This white surface had the aspect of an oversoaked membrane which has become/
become absolutely rotten." In another case he tells how the slough separated easily when scratched by the nail, without being felt by the child.

More interesting in the present connection is a description by Samuel Bard of an American epidemic in 1789 of "Sore Throat Distemper." The cases described are undoubted diphtherias: and yet "the first symptoms, in almost every case, were a slightly inflamed and watery eye, a bloated and livid countenance, and a few red eruptions here and there upon the face." In certain cases an eruption of red pimples occurred behind the ears; these were associated with great itching and profuse discharge, and later with the formation of sloughs like those on the throat.

(b) 1821 and subsequently. In 1821 Brettonneau read to the Académie Royal de Médecine his first memoir on "Croup and Malignant Angina," and focussed the attention of subsequent observers on the essential lesion by the name of "Diphthérite" which he gave to the disease. While this was an advance whose value can hardly be overestimated, it gave rise not unnaturally to two erroneous tendencies
I. too much stress was laid on the local condition.
II. too little attention was paid to the other manifestations./
manifestations.

I. The term "diphtheritic" was applied haphazard to every case where a "false membrane" appeared on the buccal mucous surface, irrespective of its nature. Empis writing in 1850 and referring to this, says "If in a child at the breast, affected with enteritis, the mucous membrane of the mouth is seen covered with a whitish pseudo-membranous layer, it is Diphthértite! A Phthisical patient, in the last stage of marasmus and emaciation exhibits as the last complication an eruption of muguet on the tongue and the mucous membrane of the mouth, and it is Diphthértite! If in a patient attacked with Scarlatina the specific cause of the buccopharyngeal inflammation is seen to produce a plastic and pseudo-membranous exudation, it is still Diphthértite! I shall not pursue further the enumeration of all the exudations to which we every day hear the denomination of Diphthértite applied."

II. The second consequence (which is still with us: the first has been removed by the discovery of the Klebs-Loeffler Bacillus) the want of attention to, or deliberate ignoring of (in especial) the skin lesions in diphtheria, is easily understood. For centuries diphtheria had been/
been confounded with many varieties of disease which were essentially eruptive, in which the most constant and diagnostic feature was a rash: now it was recognised that in diphtheria the constant feature was the membrane, and skin rashes comparatively inconstant: what more natural than that diphtheria should be definitely labelled "non-eruptive" and the existence of specific diphtheria rashes denied?.

It was not till 1858 that Germain Sée described to the Société Médical des hôpitaux de Paris certain cutaneous eruptions which he had observed in some of his cases of croup and diphtheria. He regarded them as essentially the result of the diphtheritic poisoning. The nature of the eruption varied but presented two characteristic forms:

I. Scarlatiniform.

II. Roseolar.

An interesting feature was the frequency with which the eruption occurred - in 25% of the cases.

Exception was taken to Sée's results: the scarlatiniform eruptions were regarded by some as indicating undiagnosed scarlatina. (Though in at least one of his cases true scarlet fever developed six months after the appearance of a diphtheritic scarlatiniform rash, thus indicating the non-scarlatinal nature of the latter). The high proportion/
proportion was also regarded as unusual, even by those who agreed that diphtheria rashes did occur as characteristic phenomena of the disease.

In 1859 Jonathan Hutchinson records in the Ophthalmic Hospital reports a case of ocular diphtheria in a six months infant. Both the eyes were destroyed. On the 3rd day there was a rash on the child's chest: it consisted of scattered minute red spots but more resembled certain forms of lichen than the rash of scarlet fever. On the 4th day the rash had disappeared.

In 1859 also, Greenhow records a case of wound diphtheria associated with a localised purpuric rash. "On the dorsal aspect of the left thumb is an irregularly shaped vesicle about the area of half a crown, which originated in a scratch received about six days ago." In this a membrane developed. On the 4th day "there is a slight watery haemorrhage from the nose ... there are several claret-coloured purpuric looking patches, varying in size from a pea to a horse bean, on the thumb, forearm, and inner aspect of the left elbow." These were paler next day and the patient seemed to be improving: but next day death occurred from heart failure.

In/
In 1860, Greenhow described the case of a girl of 17 with typical diphtheritic symptoms who on the 6th day of disease developed a rose coloured rash. "It resembles neither the rash of scarlet fever nor that of measles; but consists of closely aggregated rose coloured spots, about the size of fleabites, resembling the maculae of typhoid fever, like which also they disappear on pressure, but return almost immediately. Those on the face are grouped in irregular patches" (the patient had measles several years before) "those on the chest and arms are equally distributed over the skin, but most thickly upon the arms." Next day "the eruption is paler upon the face but has extended over the trunk and lower extremities, though more sparsely than on the arms and chest. Numerous Sudamina, giving a roughness to the skin, are now also intermingled with the other eruption." Next day the rash was gone.

In 1876 Sanné published at Paris his work on "Diphtheria, Croup and Tracheotomy:" and in this he takes up the question of eruption in diphtheria. After referring to the writings of Germain Sée, he makes some interesting observations on the diagnosis of diphtheria rashes from those of the eruptive fevers:- "While accepting as demonstrated the existence of diphtheritic eruptions analogous to those/
those observed in typhus, typhoid, cholera, rheumatism, etc., it is necessary, in order to be correct in declaring the diphtheritic nature of an exanthema, to proceed by exclusion, and to exclude all other causes. Now, the age of the patients, when they are children, and their sojourn at the hospitals, are conditions which strongly contend in favor of eruptive fevers. The younger the patient the greater are the chances of an eruptive fever. And first, it is indispensable to exclude all eruptions which appear before the false membranes; it is more legitimate to consider them as the primary disease of which diphtheria would be only a secondary symptom; as to those which arise during the course of diphtheria, they should, in order to be considered as manifestations of this disease, appear at a period as near as possible to the onset of the diphtheria, or at least to the entrance into the hospital; it is ordinarily in the ward of the hospital that patients contract eruptive fevers which complicate the disease for which they have been admitted." Luckily such infections are not quite so common in modern hospitals.

"The eruptions which appear at a late date should not, any more than the others, present any of/
of the symptoms peculiar to measles or scarlet fever—ocular, nasal, pulmonary and intestinal catarrh for the former; or redness of the throat, cutaneous and lingual desquamation for the latter. There should be no fever, or fresh febrile paroxysm at least, at the time the eruption appears. While these conditions should not inspire absolute confidence (for scarlatina, especially, presents in its course and appearance irregularities more or less unexpected) they are, nevertheless, quite important elements of probability. If one could establish the previous existence of the eruptive fever whose exanthema is present, or if one knew that the patient subsequently developed the fever in question, there would then be, at least respecting scarlatina, a certainty almost complete." He quotes in this connection (1) the case of See mentioned above—of diphtheria + scarlatiniform rash followed six months later by scarlatina: and (2) a case of his own, where measles was followed by diphtheria + a measly eruption.

He refers to the diagnosis of diphtheria rashes from drug rashes: "while the balsams are quite largely employed in the treatment of diphtheria, one should bear in mind, in patients so treated, the possibility of a copaivic eruption. In taking account/
account of these various causes of error (eruptive fevers and drugs) we considerably reduce the number of eruptions really due to diphtheria. In the large number of cases which I have examined I have found the exanthemata in only one fiftieth of the cases." (Contrast Germain Sée, who describes them in 22% of his cases).

He describes a variety of rashes: - "They have assumed various types. The most common has been the scarlatiniform, the only one that Sée had first in view. Others follow which present all the physical characteristics of measles, erythema limited to the trunk or the extremities, or generalized; urticaria, ecthyma, etc. Sometimes they are vesicular. These eruptions have appeared from the first to the seventh day of the disease, and from the second to the third after admission to the ward, when the patients were observed at hospital. These limits have very rarely been exceeded. Their duration was always short, a day or two at most. They were never ushered in by general symptoms. Fever, or increase of the febrile movement already existing, vomiting, anorexia, pruritus and tumefaction were absent.

As to their prognostic value, he is inclined to/
to agree with Sée who regarded them as of favourable significance. Sée stated that out of every three of his cases who developed an eruption, two recovered. Sanné gives the following proportion of recoveries in the different forms of rash:

I. Scarlatiniform  2 recovered out of 3
II. Erythematous    4 "    " " 5
III. Rubecular       1 "    " " 2
IV. Urticaria        - Always fatal.

Sanné's general conclusions are worth recording

I. Exanthemata are observed in the course of diphtheria which appear to be true cutaneous manifestations of the disease.
II. These eruptions are relatively infrequent.
III. They are met with in the grave cases as well as in the slight.
IV. Their appearance does not modify the development of the diphtheritic process.

Bourges, writing in 1892, refers to the erythemas etc., met with in diphtheria, and gives a description of the physiological mechanism concerned in their production:

"On sait que chaque artériole de la peau irrigue un petit territoire circulaire, l'artériole s'épanouissant/
s'Épancuissant en ramifications en forme de cône dont la base est tégumentaire. Si une artériole se paralyse, tout le territoire correspondant se congestionne et forme une tache rosée ou rouge. Au début d'un érythème la congestion se montre en général à un degré inégal dans ces différents territoires vasculaires: c'est ainsi qu'on voit des zones plus pâles séparant les taches rouges, avant que l'érythème ne soit généralisé. Lorsque la pression sanguine s'égale au niveau de tous les territoires vasculaires, la coloration de la peau devient la même partout, on a l'érythème scarlatinoide: et, s'il se fait de l'exsudation sous l'épiderme, il se formera en même temps des vésicules ou des bulles. Quand la congestion reste limitée à de petits îlots séparés, mais qu'elle est très active, il se fait de l'œdème et de la diapédèse dans les zones hyperémiées; l'éruption prend alors l'aspect papulo-tuberculeux. Si la pression vasculaire devient trop forte dans les territoires qu'a envahis l'érythème, les hématies sortent des vaisseaux et il se forme de l'érythème purpurique.

Sevestre and Martin in their sketch of Diphtheria for the "Traité des Maladies de l'Enfance" (Paris 1897) have given an excellent description of/
of the diphtheria rashes. They refer to the memoir of Sée and to the doubts which were cast on his conclusions: and add"Aujourd'hui ils sont admis pas tout le monde et les travaux de Unna, Fraenkel, Robinson, ceux de Hutinel et de Mussy ont permis de préciser leurs caractères et leur nature."

Their description, which includes those secondary eruptions probably due to streptococcus infections, is as follows:-

"Les érythèmes peuvent se montrer dans les premiers jours de la diphthérie ou à une époque plus ou moins tardive; ils peuvent alors être annoncés par une élévation de la température qui monte de 1 degré ou même plus. Ils ne se développent pas en un point quelconque du corps, mais spécialement dans certains lieux d'élection, qui sont par ordre de fréquence:-

1. les poignets,
2. les cuisses,
3. les genoux,
4. les malléoles;

on peut les voir aussi à la partie supérieure des fesses, à la poitrine, rarement au cou et plus rarement encore à la face. Ils peuvent paraître soit dans l'un de ces points isolément, soit dans plusieurs/
plurieurs à la fois, et généralement sur des points symétriques; souvent ils se manifestent par poussées successives à quelques heures ou à un ou deux jours de distance.

L'éruption peut se présenter sous des apparaences diverses; la plus commune affecte les caractères de l'érythème polymorphe et apparaît sous forme de petites taches de la grosseur d'une tête d'épingle ou de plaques plus ou moins larges, à limites diffuses, de coloration rose ou rouge vif, disparaissant par la pression; d'autres fois les taches ont des contours nets, circinés ou marginés, avec un centre pale et des bords d'un rouge vif; les éléments eruptifs s'étendent par la périphérie, se rapprochent les uns des autres et finissent par former des grands placards irréguliers avec quelques intervalles de peau saine. Ailleurs encore, les éléments eruptifs sont saillants et restent en général plus limités. Cette éruption a une durée assez courte, de 1 ou 2 jours en général, rarement 3 ou 4; elle disparaît progressivement en laissant quelquefois une tegère teinte brunâtre.

Quelquefois l'éruption ressemble, à s'y méprendre, à celle de la rougeole mais ne tarde pas à se modifier en prenant les caractères de l'érythème polymorphe;
polymorphe; d'autres fois, au contraire, on observe une éruption scarlatiniforme, mais celle-ci est presque toujours consécutive à l'une des éruptions précédentes; localisée primitivement aux lieux d'élection que nous avons signalés, elle ne tarde pas à se généraliser et ressemble alors d'une façon plus ou moins frappante à l'éruption de la scarlatine. Le plus souvent, le diagnostic n'est guère possible qu'en tenant compte des commémoratifs et de l'évolution de l'exanthème, lorsqu'on a pu la suivre depuis le début. Quelquefois aussi on trouve un érythème scarlatiniforme desquamatif récidivant. Enfin dans quelques cas on a signalé (Fraenkel) un érythème purpurique, caractérisé par l'existence de taches hémorragiques, de la grandeur d'une tête d'épingle très fine à une lentille, reposant sur un fond rosé et existant ordinairement dans les mêmes points que les éruptions précédentes.

Toutes ces éruptions peuvent d'ailleurs être observées dans le cours d'autres maladies infectieuses (fièvre typhoïde, choléra, septicémie puerpérale, érysipèle etc.) et les recherches bactériologiques semblent démontrer d'une façon positive leur connexion avec une infection secondaire/
secondaire qui est ordinairement due au streptocoque. Dans la diphthérie, elles se voient surtout dans les formes associées, mais peuvent se montrer cependant dans des diphthéries considérées jusqu'alors comme des diphthéries pures; en effet si l'examen bactériologique pratiqué au début a révélé seulement l'existence du bacille de Loeffler, cela ne veut pas dire que le streptocoque ne puisse plus tard intervenir et exercer une influence secondaire. Quant à la pathogénie intime de ces éruptions, elle est encore assez mal déterminée: nous n'y insistons pas."

Primary Rashes observed in the present series.

Among my own cases, a rash occurred in eight for which no possible cause seemed to be ascertainable except the poison of diphtheria. It took the form of

I. a rose-coloured scattered papular eruption in six cases.

II. an erythema multiforme in two cases.

1 An illustrative case in the first class is the following:-
A boy of 13 years was admitted to hospital with a typical diphtheritic patching on both tonsils. A bacteriological examination revealed Klebs Loeffler bacilli in practically pure culture. There was no marked constitutional disturbance. 3000 units of antitoxin were given, the throat rapidly cleared up, and convalescence was uninterrupted. On the second day in hospital (the sixth from the commencement of the disease) an eruption of small raised isolated papules, of a delicate rose pink colour and slightly larger than a pin head, appeared on the/
on the chest. There was no rise in temperature. A few hours later similar rosy papules had appeared on the inner aspect of the elbows: the rash though scattered on the chest maintained a beautifully symmetric distribution throughout. The eruption was best marked in the evening: the following morning it was gone.

No drugs such as antipyrine or the salicylates had been given: there had been no need for the administration of enemata as the bowels had moved freely and naturally: no vestige of a rash appeared in the neighbourhood of the injection, which was made under the right shoulder blade.

In the second class, the following is typical: A man of 27 years was admitted with a filmy patch on the left tonsil and a marked white patch on the left side of the uvula. Klebs Loeffler Bacilli and a very few staphylococci were obtained in bacteriological examination.

On admission there were observed several irregular splatches of erythema in the neighbourhood of the elbows and wrists. In a few hours these had extended, spreading peripherally, and new areas were seen on the back and chest and abdomen. As they spread/
spread the lesions met each other and coalesced, giving a uniform redness, except for those regions which were the centres of the original patches and which had faded leaving pale islands.

The eruption was visible for two days, and disappeared gradually. It did not extend to the legs.

Here as in the previously quoted case there was no drug or enema to account for the condition: and antitoxin had not been given.

General conclusions regarding Primary Diphtheritic Rashes.

I. The occurrence of such rashes is proved beyond all possibility of dispute by the historical evidence available.

II. Many varieties of eruption may occur -

Delicate Rose red papules

Erythema multiforme

Urticaria

Erythema scarlatiniforme

being the most commonly met with. The duration varies: and averages two days.

III. The frequency of their occurrence is probably far greater than is capable of definite proof.

There/
There are so many secondary factors introduced in diphtheria that it becomes impossible to say what rashes are due to these and what are primarily diphtheritic. Antitoxin is given in every case: enemata have very frequently to bulk large in the treatment of a disease where gastric irritation must be studiously avoided.

The percentage of undoubted diphtheria rashes in my cases is comparatively small - 2%: but they probably represent only a part of the total. It is impossible to help believing that they are but the indication of a comparatively large number which, occurring later in the disease after the giving of antitoxin, are - in consequence - generally included among the antitoxin rashes.

The following table shows percentages as recorded:

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<th>22</th>
<th>SEE</th>
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<tr>
<td>72</td>
<td>SARTE</td>
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<tr>
<td>39</td>
<td>GASSICOURT</td>
</tr>
<tr>
<td>120</td>
<td>MUSSE</td>
</tr>
<tr>
<td>2</td>
<td>PRESENT SERIES</td>
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IV. Prognostic significance. In the present series, every case recovered. It is probable that a skin eruption (excluding haemorrhages) is to be taken as a sign of reaction on the part of the individual.

Note regarding Cutaneous haemorrhages in Diphtheria.

The occurrence of skin haemorrhages - varying from minute petechiae to large purpuric patches, in the neighbourhood of the joints or extending over the trunk - is always of grave significance in diphtheria. Such haemorrhages are seen early in fulminant cases, or towards the end in severe cases with marked prostration.

They were observed in five cases of the present series; all five ended fatally.

The following case illustrates this form of rash:-
A girl aged five years was brought into Hospital suffering from diphtheria. From her appearance it was obvious that she was profoundly ill: the face was of a bluish pallor, the head was held stiffly with the mouth open: the breath (the odour of which was typically diphtheritic) came noisily through the open mouth. An examination of the fauces revealed greyish irregular patching. There was marked enlargement of the glands of the neck. Abundant/
Abundant Klebs Loeffler's Bacilli were recovered from the throat, and from the nose which was discharging thickly.

In spite of repeated doses of antitoxin - 38,500 units being given in all - there was never any appearance of reaction: and on the ninth day after admission to Hospital death occurred.

On the day before death, a few small widely scattered haemorrhagic spots appeared on the chest and abdomen - about the size of a lentil and dusky bluish in colour. On the back, and behind the thighs and at the elbows, a diffuse bruised appearance of the skin was seen, which became more marked as death approached. During the last three days the discharge from the nose was sanious.
Secondary Rashes in Diphtheria.

Having discussed the occurrence of Primary Diphtheria Rashes, and having concluded that they are frequently met with and varied in nature, we pass to a consideration of the rashes due to Secondary Causes: and these we shall deal with in the following order.


II. Antitoxin Rashes.

III. Rashes of Intercurrent Eruptive Fevers

(These two it will be suitable to discuss together)

IV. Enema Rashes.

V. Drug Rashes.
Secondary Rashes in Diphtheria.

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II. Antitoxin Rashes.

III. Rashes of Intercurrent Eruptive Fevers
    (These two it will be suitable to discuss together)

IV. Enema Rashes.

V. Drug Rashes.
Streptococcic Rashes.

The frequent occurrence of isolated phenomena about the twelfth or thirteenth day of an attack of diphtheria was first called attention to by Sevestre and Martin. These phenomena consist of a rash - most frequently scarlatiniform, but in a few cases erythematous - joint pains, albuminuria etc: with more or less general constitutional disturbance.

Sevestre and Martin, and also Roux, suggested that the frequency with which these phenomena developed on or about the thirteenth day seemed to indicate that they were the symptom-complex of a secondary disease, with an incubation period of thirteen days, the infection occurring at the time of invasion of the diphtheria.

They further suggested that the cause was organismal and probably streptococcic: reasoning from the fact that they frequently found evidence of mixed infection in the bacteriological examination of the throats of these cases, and that they occasionally found them develop in pure streptococcic infections of the throat.

Antitoxin they were inclined to believe had the effect of lowering the resistance of the organism/
organism to the attacks of this secondary infection, just as suppuration is more liable to occur in a part poorly supplied with blood.

Streptococcal Rashes in present series.

In the present series, eighty consecutive cases were specially studied in relation to this question. I made a careful bacteriological examination of the throat of each case on admission (incubating on blood serum in the usual way) and at intervals during the stay in Hospital.

In nine of the eighty cases a marked streptococcal infection of the throat was found at one time or other, in the course of the disease: and, out of these nine, five developed symptoms, corresponding to those described by Sevestre and Martin, about the 13th day. In the cases where no streptococcal infection of the throat was at any time found, two showed epiphenomena about the thirteenth day.

In other words 55% of the streptococcal cases developed 13th day symptoms.

2.8% of the non-streptococcal cases developed 13th day symptoms.
Or, shown diagrammatically:

These results seem to indicate that there is some connection between the streptococcus infection and the 13th day phenomena. As to the part played by antitoxin in lowering the resistance of the organism to the streptococcic invasion, it appears to be as probable that the lowered resistance is due to the diphtheria bacillus or its toxines, acting locally and generally.

The following cases are illustrative:

1. First Case.

A woman aged 21 was admitted with marked inflammation of both tonsils and a slight filmy patching on their inner surfaces and on the uvula.
Swabs taken from the throat showed a few polar-stained Klebs Loeffler Bacilli, and streptococci in long chains.

The temperature reached the normal in six days, during which time the throat symptoms gradually cleared up.

On the 13th day albumen appeared in the urine, and a fine punctate rash was seen covering the chest, upper part of the abdomen, upper arms and back: very/
very closely aggregated. There was no sickness or headache, and the tongue was not furred. Sore throat was not complained of; examination revealed streptococci still present: no diphtheria bacilli. The albumen lasted for two days: the rash was of short duration, being practically gone on the evening of the day when it appeared.

2. Second Case.

A boy of nine years came in with a localised patch on the right tonsil. Swab showed Klebs-Loeffler and a few streptococci.
The throat cleared up rapidly. On the eighth day an urticarial antitoxin rash developed, lasting 48 hours.

On the thirteenth day patient complained of some pain in the throat, and of pain in the left elbow and shoulder and right shoulder. In the evening the temperature rose to 100.8. Examination of the throat showed pure culture of streptococci.

The next day the temperature was down, the throat was not painful, and the joint symptoms though still present in the left shoulder and elbow were much less severe. On the fifteenth day patient was quite well. Swab of throat showed a few streptococci still present.

(Note: Weill and Degny have described cases with similar throat symptoms under the name "angines de retour.")

3. Third Case.

A case where otorrhoea developed on the thirteenth day of disease is the following:-
A boy aged 2\(\frac{1}{2}\) years was on admission to hospital found to have red swollen tonsils with some indefinite patching. Bacteriological examination showed diphtheria bacilli, streptococci and staphylococci. The temperature which was 102.4°F on admission reached the normal on the third morning, and the local symptoms cleared up.

Convalescence was uninterrupted, except that on the morning of the thirteenth day the child became/
became restless and fretful. When the right ear was examined he cried and was evidently suffering some pain. In the afternoon discharge came from this ear and relief was experienced at once. The discharge continued till the 15th day and then stopped.

Examination of the discharge revealed streptococci and a few rods (Klebs-Loeffler? staining not good).

**Summary of the seven cases.**
The following is a brief summary of seven cases where 13th day phenomena were observed.

**(A) Streptococcal Cases.**
1. Punctate erythema + albuminuria.
2. Punctate erythema
3. Punctate erythema + rise of temperature.
4. Sore Throat + Joint pains + rise of temperature.
5. Otorrhoea.

**(B) Non-Streptococcal Cases.**
1. Erythema multiforme.
2. Punctate erythema + rise of temperature (99.8)
Antitoxin Rashes.

The varieties of rashes which may result from the injection of antitoxin and the frequency of their occurrence, have been variously described and estimated by different writers.

**Frequency.**

I. The Metropolitan Asylum Board give the following figures:

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1898</td>
<td>45%</td>
</tr>
<tr>
<td>1899</td>
<td>34%</td>
</tr>
<tr>
<td>1900</td>
<td>43%</td>
</tr>
<tr>
<td>1901</td>
<td>43%</td>
</tr>
<tr>
<td>1902</td>
<td>47%</td>
</tr>
<tr>
<td>1903</td>
<td>45%</td>
</tr>
</tbody>
</table>

or an average of 43% for the six years: never much above or below this average.

II. The Investigating Committee of the Clinical Society of London report a rash in 35% of their cases.

III. Hartung has summarised the observations of certain European Hospitals and finds rash reported in 11% (this in 2661 cases).

IV. Berg, in 337 cases which he studied in the Willard Parker Hospital in New York, got a percentage of 24.

V. The City/
V. The City Hospital, Edinburgh, reports for 1906 give 15 percent of antitoxin rashes.

VI. Rolleston writing in 1905 records the remarkably high percentage of 74, in 600 cases studied at the Grove Fever Hospital.

VII. In my own cases, antitoxin rashes were observed in 14% of the cases: that is 53 in all.

From this it appears that a considerable difference exists among the results of observers.

Possible reasons for these varied results:

I. The improvement in the quality of the antitoxic serum of late years has had the effect of reducing the unpleasant sequelae of injection. More concentrated sera are being produced; and experiments have been made with a view to discovering/
ing whether filtering the serum, to free it from certain toxalbumins, is of value: another suggestion being that it is advantageous to heat the serum before administration.

Antidiphtheria serum has three elements in its composition.

1. Horse Serum.
2. A small amount of preservative.
3. The antitoxic principle.

1. It is generally taken for granted that the horse serum is the cause of the after effects of antitoxin; and certainly the injection of horse serum alone into the subcutaneous tissues has been followed by the appearance of rashes etc.

2. Experiments to ascertain the part played by the preservative have always proved negative. There is no reason to expect that the very small amount of mild antiseptic present could produce such general effects.

3. The question whether the real cause of "antitoxin rashes" may not be to some extent the antitoxin itself is discussed later (Page 43)

II. Varying standards of observation and diagnosis. Rolleston's results give such high figures as would seem to suggest that the most transient cutaneous phenomena have been included. On the other hand,
the figures in the present series refer only to cases where the diagnosis of "antitoxin rash" has been made after every other possible cause of the eruption has been excluded.

III. The use of different sera. It is a matter of common experience that the serum produced by certain firms is much more liable to cause rashes etc., than that of other firms. In the present series, one variety of serum was used in practically all the cases: a variety which experience has shown to be comparatively free from unpleasant results.

IV. Accurate dosage. When antitoxin was first introduced there were many who regarded its use as "little short of homicide." Its value however soon became evident: and now it is the withholding of serum that is regarded as homicidal. With the increase in popularity of serum, and the announcement that its administration was unattended by risk, it became common to give large and often enough excessive doses. It was thought better "to err on the safe side." But it is better still not to err at all: and lately the tendency has been for the dosage to settle down towards a recognised standard, so far as that can be arrived at where the individual judgement of the physician must/
must come in to estimate the strength and resisting power of the patient. The facts on which this standardisation is based are the extent and position of the diphtheritic lesion, modified by the previous duration of the disease and the general condition of the patient. Even though antitoxin were innocuous, it would be a good thing to have a standard dosage.

But it is known that antitoxic serum is not innocuous; unpleasant results follow its use. And while it is generally postulated that these results are due to the horse serum, and that they will be gradually diminished, if not entirely removed, as a more concentrated product is put on the market, this postulate is worthy of consideration before being granted.

Putting aside the question as to whether the number of paralyses has been increased by the use of antiserum we shall here consider whether the blame for the common "antitoxin phenomena" is not to be laid in part to the charge of a superfluity of the antitoxic principle.

Bacteriological investigations have proved that where too much antitoxin is given, more than is required to neutralise the toxin present, the free antitoxin takes on the action of a toxic substance; and/
and indeed the organism makes provision for defending itself against this new poison by the formation of a new anti-body - an anti-antitoxin. Is it unreasonable to suppose that this superfluous antitoxin is capable of producing harmful effects, and of giving rise to part at least of those reactions of the organism which are known as antitoxic rashes?

This is however not merely a supposition, as a consideration of the following facts will show:

1. Rashes are frequent and severe after an overdose of serum.
2. Rashes are relatively frequent and severe in cases where little or no diphtheria is present, or after prophylactic injections.
3. Rashes are very infrequent in severe toxic cases, although large quantities of antitoxin are given.

1. An overdose of serum is very frequently followed by severe and continuous rashes, joint pains etc. In the present series of cases I have on four occasions had this fact emphasised. They were the only cases where the amount of antitoxin given did not correspond as accurately as could be judged with the requirements of the case: and in all four a copious eruption came out, in every case above the/
the average in intensity, and in one case affording the most marked example of "antitoxin" disturbance I have seen.

I shall quote two of the cases.

(a) This patient, a lady, had been given a full dose of antitoxin before admission to hospital. Unfortunately however this fact was not ascertained and a further injection was given. The local symptoms had never been very marked.

A few days afterwards a copious urticarial rash came out on the trunk and limbs; it gave rise to great irritation, nausea, and some rise of temperature. (The chart has been mislaid so cannot be given here) Crop after crop of the eruption showed itself, the itching being very distressing and continuous.

(b) The second case was a boy of five years who came into hospital with a small patch on one tonsil. 1500 units A.D.S. were given.
Later in the day another boy of the same age was admitted, with severe symptoms. By a mistake, owing partly to a changing of bedsteads and partly to a strange nurse having just come on duty in the particular ward, the first boy was again prepared for antitoxin, and received 6000 units intended for the other.

Four days later an urticarial rash showed itself all over the trunk and lower extremities.
There was great itchiness. The rash came in successive crops for three days and then disappeared: the temperature having risen to 101.2° on the second day.

After a clear day, the eruption again broke out, even more intensely irritable than before. To add to the suffering of the child, the joints became painful: first the elbows and wrists, then the shoulders, knees, and left ankle: the slightest movement of the joints caused great pain. The temperature rose to 103.4° and continued up for four days, during which time the rash kept "coming out and going in." It did not attack the face at all. Albumen was present in the urine during the last four days of the rash and on the third day there was a trace of blood.

2. In very mild cases of diphtheria and especially where the diagnosis of diphtheria has been at fault; and also in cases where a prophylactic injection of serum has been given - in such cases the sequelae of antitoxin tend to be very marked.

W. P. Herringham, in his article on Diphtheria in Clifford Allbutt's System of Medicine, quotes three cases which really illustrate the present subject. Talking of pain in the joints and muscles/
muscles as a result of antitoxin, he says:

"Dr. Newton Pitt has told me of three such cases - a child, his mother, and his nurse - who were for two or three days in such excruciating pain that they could hardly bear any one to move in the room, and were quite unable to take food. They said that they had never felt so ill in their lives. None of them, as it happened, had diphtheria at all for the treatment was carried out on a bacteriological report which was afterwards recognised to be at fault."

3. In severe cases of diphtheria, where massive and often-repeated doses of antitoxin have been given, antitoxin rashes are comparatively uncommon.

In those of my cases which had over 12,000 units of antitoxin (excluding those cases which died before a rash might be expected to appear) the incidence of rashes was only 8%: as contrasted with 14% over all. That this is due to some extent to want of reaction on the part of the patient may be true: but when the relatively huge amount of horse serum which has been injected is remembered, we should expect the percentage of cases of rash to be higher than 8% at any rate.

Rolleston has said "the frequency and intensity/
intensity of rashes and other serum phenomena are in
direct relation to the size of the dose, and in
inverse ratio to the character of the diphtherial
attack."

**Average Day of Antitoxin Rashes.**

In my series the bulk of the eruptions occurred
between the 7th and 12th days after injection: the
average day being the 9th. What were apparently
typical urticarial antitoxin rashes showed in one
case as early as the 3rd day and in another case as
late as the 20th day after injection.

The investigations of the Clinical Society of
London produced the following figures: out of 633 cases

- 33 had a rash between 1st and 6th days.
- 147 " " " 7th ad 12th "
- 34 " " " 13th and 18th "
- 6 " " " 19th and 31st "

**Varieties of Antitoxin Rashes.**

The following varieties of eruption have been
attributed to antitoxin:

- Urticaria.
- Simple Erythema.
- Circinate Erythema.
- Scarlatiniform Erythema.
- Morbilliform rash.
- Petechial Rash.
- Mixed rash.
In this series the fifty-three rashes observed were classified as follows:

- Urticaria: 38
- Erythema, Simple or Blotchy: 6
- Erythema, Scarlatiniform: 4
- Erythema, Circinate: 0
- Morbilliform: 2
- Petechial: 0
- Mixed: 3

It is interesting to note how the relative frequency changes. Stanley describes in 1902 (B.M.J. Feb. 19th) a circinate erythema as being the anti-toxin rash. In 1905 Rolleston finds urticaria most common, with circinate erythema second. Stanley's circinate was often accompanied by a slight fever; Rolleston's was seldom so accompanied. The Clinical Society of London in 633 cases had:

- Erythema: 161
- Urticaria: 37
- Mixed: 17
- Petechial: 5

Fever occurred in 136 cases.

Now urticaria has come to the front as the most common/
common antitoxin rash: circinate erythema is comparatively seldom observed.

Varieties of Antitoxin Rash described individually.

I. Urticaria.

This takes the form of raised wheals white in colour and resistant to the touch. The white wheals are surrounded by a red zone. At first regular in outline, the lesions in spreading take on a most irregular shape, so that a serpiginous appearance is presented. At this stage, one finds pale rounded wheals in the midst of a rose red depressed area with serpiginous edges; so that a cross section of the skin would give the appearance shown in the diagram.

The eruption varies in intensity: it may be very violent, with much swelling and oedema of the surrounding parts; in which case the accompanying constitutional disturbance, sickness and vomiting, nausea, shivering etc., may be distressing.

Locality/
Locality and Distribution.

Most commonly the rash appears first in the region of injection - under the shoulder-blade or on the abdomen as the case may be. It rapidly spreads however so that it is sometimes difficult to tell what the starting point was. The face is generally unaffected.

Frequency.

Urticarial rashes made up 72% of the antitoxin rashes observed in my series. As has already been stated, the frequency varies greatly in the accounts of different observers.

Day of Occurrence.

The average day of occurrence was the 9th after injection: the earliest case occurred on the 3rd day, the latest on the 21st.

Individual Susceptibility.

The question (which has not to my knowledge been discussed) as to whether certain individuals are more prone to develop these rashes than others naturally arises when we remember that urticaria as a disease exhibits a remarkable tendency to occur in a particular victim as the result of a particular cause. Thus while a nettle-sting gives rise to urticaria in most people, there are some on whom it/
it has no effect. Certain articles of food—as for example pork, oysters, rhubarb—are well known to invariably produce urticaria in certain individuals and never in others. In the same way an oedema of the glottis may be brought almost instantaneously by the eating of fish. Some powerful influence is exerted by these substances over the contraction of the vessels of those who are susceptible to them. It seems probable that antitoxin may in a similar way have its preferences, and select particular individuals in whom to produce urticaria. Two of my cases had had previous attacks of diphtheria: one had a marked urticaria on both occasions, the other had none.

**Duration.**

The average duration was two days. (In Rolleston’s series it was 3.9) In some cases it was very transient, lasting one or two hours. In one case (that quoted on Page 45) it was present seven days in all.

**Influence of Age and Sex.**

There was practically no evidence that these had any influence whatever.

**Accompaniments.**

1. **Rise of temperature.**

This was present in only a small proportion of
the cases, and was entirely absent in several where the rash was well marked and widely distributed.

The returns of the Metropolitan Asylums Board for 1895 record a rise of temperature in 30% of antitoxin rashes. This percentage seems to be steadily decreasing.

2. Irritation and Itching.

Itching is always present to some extent, and may become almost serious in its intensity, especially in those cases who have been run down before contracting diphtheria and whose nervous system is debilitated. A preparation such as that suggested by Rolleston (a drachm of menthol to the ounce of white paraffin) gives relief in most cases.


Five of the cases which showed a urticarial rash had joint pains simultaneously. They are discussed later.

Illustrative cases.

1. Urticaria with rise of Temperature.
This rash occurred in a child of 14 months who was admitted with faucial diphtheria. 4000 units A.D.S. were given on admission: and on the seventh day in hospital a further injection of 3000 units was given as there seemed to be a tendency to the formation of fresh throat exudation.

On the evening of the 13th day an urticaria came out, beginning at the seat of injection and spreading over the trunk. It faded before morning: but/
but fresh crops came out the next day: in the evening it was very bright. The following day it was strongly marked on the back and legs. A photograph was taken with difficulty, as the exposure to the air increased the irritation.

Next day it was less profuse but the serpiginous limits of the patches were defined with remarkable distinctness.

The temperature was elevated throughout, reaching as high as 103. The day after the fading of the rash it dropped.

2./
2. Urtriciaria without Rise of Temperature.

This case is typical of the urticarial antitoxin rash usually met with. The patient, a girl of seven, had 6000 units on admission. Seven days later an urticarial rash appeared on the back, spread over the trunk and down the legs. It came and went for two days. There was considerable itching, but no rise of temperature or pulse rate.
2. Scarlatiniform Rash.

Rashes resembling the eruption of scarlet fever occur so frequently from a variety of causes - drugs, enemata, a hot bath, to mention but a few - and as prodromal and concomitant rashes in the various eruptive fevers such as Chicken pox and Measles, that it is doubtful how many of the scarlatinal rashes ascribed to antitoxin have really it as their cause. Excluding those very transient rashes localised round the point of injection, I have notes of only four cases out of the 380 where a generalised scarlatiniform rash could be regarded as almost certainly antitoxic in origin.

Berg, who found 4 scarlatiniform rashes out of 33 consecutive antitoxin rashes, associated them with a severe type of diphtheria. This has not been my experience.

**Distribution.**

The rash begins at the seat of injection, spreads down the back and round to the chest and abdomen, down the arms and legs. (This spread is usually discontinuous - thus the thighs may be missed and the rash appear on the leg below the knee). The face is as a rule not involved. Successive crops usually occur. In three of my four cases, there/
there was a distinct tendency for the rash to fade rapidly and rapidly brighten up again, in a way that is not common in scarlet fever.

Desquamation.
This occurred to an appreciable extent in two cases, in one of which there had been some miliaria alba. It was fine and branny in character, resembling the desquamation in measles: in true scarlatina, while the desquamation on the trunk is of this nature, that on the hands and feet is typically scaly. In the "erythema scarlatiniforme" described in Dermatology the desquamation on the other hand is profuse, the skin coming off in sheets.

Day of Occurrence.
This was earlier than in the urticarial rashes: being the 4th, 5th, 5th and 7th day.

Duration.
The average duration was three days.

Age and Sex.
In such a small number of cases it was impossible to tell whether these had any influence. Probably they have none.

Accompaniments

1. Rise of Temperature. This occurred in one of the four cases but had probably no connection with the rash. In the others there was no rise of temperature./
2. Joint pains have been described by different authors as frequent accompaniments of these rashes; but they did not occur in any of my cases.

Diagnosis.

The great importance of these rashes lies of course in the difficulties of diagnosis to which they not infrequently give rise. The early recognition and isolation of a case of scarlet fever, at home or even more especially in a hospital ward, being often a matter of the greatest moment. The main points of importance in diagnosis are as follows:

1. Character of the rash. The typical scarlatina rash, which is simulated by the rashes occurring in so many other conditions, differs from all of them in being what might be called a "live" rash – in the pungent heat of the skin, and in the atmosphere which it seems to have about it. It is this quality which makes it so difficult to describe in words and renders it incapable of reproduction by coloured photography. The rashes due to antitoxin and other causes are less vivid and cooler: the skin has never the pungent heat so typical of scarlet fever.

The circumoral pallor so characteristic of scarlet fever is seldom seen in the antitoxin condition.

2./
2. Locality and Itinerary of the rash.

While the antitoxin rash may have the same anatomical distribution it has not always the same method of spread as the scarlatina eruption. In the first place it almost always begins at the seat of the injection, while others as invariably first shows itself about the neck. The start of the rash is however always noticed, and a considerable area of skin may be involved before the doctor's attention is called. This suggests that it is advisable to instruct those attending to the patient to keep a careful watch on the skin round the injection, in order that should a rash develop they may be able to report as to its beginnings.

In its spread the antitoxin rash is often erratic, missing portions of skin: in scarlatina there is almost always a steady flow from the neck downwards.

3. Duration. I find it generally stated that the antitoxin rash is of short duration: in my cases its average duration was as already stated three days.

4. Disappearance and reappearance. The irresponsible coming and going of the antitoxin rash is characteristic.

5. Presence of other rashes. Stress has been laid/
laid on this as excluding scarlatina: I hardly see that it is of any importance. Mixed antitoxin rashes are fairly common: but this fact does not help diagnosis.

6. Rise of Temperature. In typical scarlatina there is a sudden elevation of temperature at the onset, to $103^\circ$ or $104^\circ$. In the antitoxin rash there is typically no rise of temperature.

7. Acceleration of Pulse rate. This is one of the most constant features of scarlet fever, the pulse running up to 120. In the antitoxin rash there is as a rule no change in the pulse rate.

8. Presence of Scarlatinal Symptoms. These are typically sickness, headache, and vomiting. The sore throat may be of little value as a diagnostic in pharyngeal diphtheria, but is useful if the pain is considerable.

9. Diazc reaction in the urine. The importance of this as a diagnostic has been emphasised by Oppenheimer and Loeper and others.

In order to estimate its value I examined the urine in 25 cases of antitoxin rash, including the four scarlatiniform cases: and in 50 cases of well marked scarlet fever in the first or second day of the rash. In all the antitoxin cases a negative result /
result was obtained. In the scarlatina cases, I got 21 positive and 29 negative; i.e., 42% positive.

From this investigation it would appear that if with a scarlatiniform eruption a positive diazo reaction is obtained, the likelihood is that the case is one of scarlet fever. But a negative result does not justify us in excluding scarlet fever, as in 58% of my cases (which were all a sharp well-marked type of the disease) the diazo was negative.

10. Desquamation. This comes rather late to be really a practical diagnostic feature, and is rather an indication of the correctness or incorrectness of a diagnosis already made. In the antitoxin rash as already stated, desquamation is absent or fine; in scarlatina it is flakey.

Summary/
Summary of Practical Diagnostic Points.

<table>
<thead>
<tr>
<th></th>
<th>Scarlatinitform Antitoxin Rash</th>
<th>True Scarlatina</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Liveness&quot; of Rash</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Localilty and Itinerary of Rash</td>
<td>from seat of injection: spread irregular.</td>
<td>from neck downwards.</td>
</tr>
<tr>
<td>Coming and going of rash.</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Rise of Temperature</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Acceleration of Pulse Rate</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Presence of Vomiting etc.</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Diazho Reaction</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Desquamation</td>
<td>Fine</td>
<td>Scaly</td>
</tr>
</tbody>
</table>

Illustrative cases.

I have described below four cases. In the first two, scarlatinitform antitoxin rash occurred - the first typical and giving no difficulty with diagnosis; the second presenting considerable difficulty. The third and fourth cases are examples of scarlet fever developing during an attack of diphtheria: the one being an obvious case, the other very atypical.
Case 1. Scarlatiniform serum rash.

A boy of eleven years, with pharyngeal diphtheria, developed a scarlatiniform rash on the seventh day after an injection of 3000 units of antitoxin. It was seen in the evening, and though it already involved the chest and abdomen as well as the upper part of the back, it was still best marked at the seat of injection - under the left shoulder blade.

There was no rise of temperature, no acceleration of pulse (this was important as the boy had had a rather/
rather unstable pulse since admission) no sickness, vomiting etc. There was no previous history of scarlet fever.

The next morning the rash was faint, but in the afternoon it came out afresh on the chest, and on the inner side of the thighs. It was fairly bright in the evening. The following day the rash was present on the arms and back and buttocks: it faded towards evening.

Case 2. Scarlatiniform Serum Rash.
A girl aged 6 1/2 years admitted with typical faucial diphtheria, tonsils unequally involved. Two injections of antitoxin were given, amounting to 10,000 units. On the fourth day in hospital a small punctiform erythema was observed at midnight. It involved the back and more faintly the front of the chest. The skin round the injection area was more strongly marked with the rash. The next morning the temperature, which had been 100.4°, had fallen to normal: but the rash was now general over the whole body except the face. For two days it remained out: during this time the pulse did not rise above 100°, and sore throat was not complained of. The next day the temperature rose to 99° in the morning and to 100.6° in the evening: there was a considerable enlargement of the glands on both sides of the neck. On the following morning there was a brilliant scarlatiniform eruption on the chest, abdomen, neck and upper limbs. The temperature was 100°. That this was a scarlet fever rash was suggested by the rise of temperature on the previous day and the enlargement of the glands: while against this probability was (1) the previous scarlatiniform eruption (the origin of which at the site of injection had been noted): (2) the absence of sickness, headache and sore throat (3) the comparative/
comparative slowness of the pulse - 120: it had been 140 with the original throat infection.

The rash was gone within 24 hours. There was no subsequent desquamation.

Case 3. Typical Scarlet fever developing during diphtheria.

A boy of five years came in with mild diphtheria. Temperature settled on second day, and throat cleared up.
up.

On the morning of the third day, the temperature rose to 100.4°; the boy was sick and complained of headache and soreness of the throat. The latter showed generalised redness on examination. The pulse had risen to 120. He was isolated on suspicion.

In the evening a copious scarlatinal rash came out on neck, chest, and back. Pulse was now 140 and temperature 103°. From this point he followed the ordinary course of a typical scarlet fever.

Case 4. Very mild scarlet fever developing during diphtheria.

While a really typical scarlatina such as the case just described can hardly escape early diagnosis, such a miniature case as the following is apt to be missed.
A little girl two years old was admitted to Hospital with diphtheritic patching on both tonsils. 3000 units antitoxin were given, and the patches rapidly disappeared leaving some redness.

On the evening of the fifth day in hospital a faint punctate rash was observed about the neck and chest. The temperature was found to be up to 100.4°; the pulse was slightly quickened. The cervical glands were just perceptibly enlarged: the tongue was coated, papillae not prominent. The throat and palate were still red and there was no punctiform appearance on the mucous membrane. The next morning the temperature was down, the rash gone and the child looked much better.

Three days later bronchopneumonia developed and the temperature was swinging for nine days.

Six days after the first appearance of the rash an unmistakeable scarlatinal desquamation began.

Fourteen days after the injection a typical urticarial antitoxin rash appeared.

3. Erythema, simple and Blotchy. Erythema may be taken histologically as the early stage of urticaria. In both there is distension of the peripheral vessels: but in urticaria serum is poured out and compresses the vessels, producing the raised/
the raised white lesions.

Erythema in the form of a diffuse redness or as scattered blotches not raised above the surface of the surrounding skin occurred as the result of antitoxin in six of my cases - 1.6%

In most it began round the seat of injection and in four of the six cases was confined to the back.


Of this condition I had no examples. Rolleston describes it as a very common phenomenon between the 10th and 18th day. "An eruption, at first amorphous, subsequently becoming circinate ... usually appears first on the knees and elbows, or on the inner side of the thighs, and though occasionally it remains limited to these sites, as a rule spreads thence over the rest of the limbs and invades the face and trunk. The rings of the erythema are at first quite small, but gradually enlarge, so that by the second or third day of the eruption/
eruption they measure a half to one inch in diameter. A variable amount of staining of the skin is left when the rash fades, which lasts for a few days and may be followed by a slight degree of branny desquamation."

5. Mixed Rashes.

In three cases two distinct varieties of antitoxin rash were present at the same time in the same patient.

In one case there was an abundant urticaria on the back and abdomen and a faint scarlatiniform rash on the inner sides of the thighs. In another, urticaria round the seat of injection was present simultaneously with a raised blotchy erythema about the buttocks (the latter eruption may however have been the result of an enema given twenty four hours previously) In the third case a blotchy erythema of the trunk occurred with a scarlatiniform appearance about the elbows and knees.

6. Petechial Rashes.

In the report of the Investigating Committee of the Clinical Society of London a petechial rash is said to have occurred in five out of 633 cases: two/
two of the five cases died.

I had no examples of such rashes.

7. Morbilliform Rashes.

These are much less common than the scarlatiniform rashes, but occasionally occur and may give rise to difficulties in diagnosis. The eruption as commonly seen is somewhat less defined and regular than the typical measles eruption. It is seen most frequently at the site of injection about the buttocks, sometimes round the knees and thighs, seldom on the face.

Morbilliform rashes occurred twice in the present series; neither case had any resemblance to measles except in the rash.

Diagnosis. 1. Catarrhal symptoms and Koplik's spots. As contrasted with scarlet fever where the rash occurs early and is often the first indication of the presence of the disease, the diagnosis in typical measles is usually made before the occurrence of the rash, in the three days of catarrh which precede it. In this period Koplik's spots on the buccal mucous membrane are to be seen and are of the greatest help in determining the nature of the case. I was able to isolate one case 36 hours before/
before the appearance of the eruption on the strength of Koplik's spots + slight catarrhal symptoms.

2. Distribution of the rash.

The face is generally avoided by the morbilliform antitoxin rash: in true measles it is always involved.

3. Rise of Temperature.

In measles the temperature has generally reached 102° by the time the rash appears. Accompanying the antitoxin eruption there is generally no rise of temperature.

Illustrative case:

The following is an interesting case where measles developed during diphtheria and where the diagnosis was obscured by the presence of an antitoxin rash.

A little girl of 3½ years developed a rash nine days after the administration of two 5000 unit doses of antitoxin.

The appearance of the rash which was erythematous in character was accompanied by a rise of temperature to 100° and a slight variation in pulse rate. The trunk alone was involved, exhibiting a blotchy dull red eruption symmetrically distributed, and spreading in large patches round from the back to the abdomen.
The temperature fell to normal two days later and remained so during the third day: but the rash which had faded and reappeared several times was now well marked on the thighs and buttocks in its original form.

The following day the temperature again rose and by evening had reached 101°. The blotchy erythema was still present on the thighs and buttocks.
buttocks, but on the chest it had been replaced by a fine punctate eruption scarlatiniform in appearance. In the morning there was a drop of temperature to 99°; no constitutional disturbance was present, and the rashes were regarded as a mixed antitoxin eruption.

But the next morning the temperature had swung up to 102°: the face, which had previously been clear, showed the beginning of a rash—small and very close but distinct spots, slightly raised, with a tendency to crescentic grouping.

The respiration was quickened from 34 to 60, and catarrhal symptoms arrived late in the form of a watery discharge from the nose and slight clearness of the eyes. An examination of the mouth revealed a profuse collection of Koplik's spots.

At this time three distinct eruptions were present:

1. A blotchy erythema on the upper thighs and buttocks.
2. A Scarlatinaform erythema on the chest and abdomen.
3. The rash of measles on the face.

The first was antitoxic in origin; its presence obscured the significance of the early rise in temperature (A) with the drop on the third day.
The second was without doubt a prodromal measles rash, and should, along with the peculiar variation in temperature just referred to, have raised suspicions of that disease.

The third, the measles eruption, soon spread over the body: and the case from this point on behaved typically.
Notes regarding the other after-effects of antitoxin. (accompanying rashes, or less frequently occurring alone).

(A) Other cutaneous phenomena.

1. Hyperidrosis.
   This has been described or a frequent result of antitoxin, occurring within an hour or two of the injection.
   While a slight degree of perspiration was common in my cases, nothing meriting the name "hyperidrosis" occurred.

B. Local Phenomena.

1. Local Pain.
   Many writers have stated that severe pain lasting for several hours is frequently experienced, especially by adults, at the seat of injection.
   This has never been my experience: when care is taken that the injection is made into the subcutaneous tissue, and not into the skin itself, pain should not be felt except for a few seconds during the actual injection.

2. Local Haemorrhage.
This is described as occurring in severe cases: in the form of petechiae appearing round the seat of injection, or subcutaneous haematomata.

3. Local Abscess.

In only one of my cases there was abscess formation: the abscess subsequently required opening. This same patient (a woman) had developed a similar abscess after injection in a previous attack of diphtheria.

In Rolleston's series abscess formation was comparatively common: he records ten cases.

C. Locomotory System.

1. Joint Pains.

In five of the cases where rash occurred (10%) joint pains were present as an accompaniment, and in four other cases they occurred without a rash. The middle sized joints - shoulder and elbows, knees and ankles - were most involved: the hips occasionally.

The percentage incidence of joint symptoms in my cases was comparatively small: 9 out of 380 cases or 2.4%. The London Clinical/
clinical Society report 40 in 633 cases, of which 35 were accompanied by a rash.

The occurrence of joint pains without a rash was not uncommon in my series. The following case illustrates this:

A man aged 20 had 3000 units A.D.S. injected. There was no rash of any kind, but on the 14th day after the injection he had severe pain on the hips and later in the right shoulder joint: no redness or swelling was present. The temperature and pulse were unaffected, and the pain passed off in 24 hours.

2. Arthritis.

Actual/
Actual inflammation of the joints with effusion is comparatively rare as an antitoxin sequela.

3. Muscle and fascia pains.
These are fairly common and have no preference for particular regions. Herringham quotes a case recorded by Szontagh where the symptoms were severe and protracted, lasting a month.

D. Haemopoietic System.

1. Adenitis.
This does not appear to be so common now as it was in the earlier days of antitoxin. In not more than two cases (one of which is referred to on Page 66) did I observe it accompanying an antitoxin rash.

2. Blood changes.
The hypoleucocytosis described by Ewing as the result of antitoxin has no relation to antitoxin rashes.

E. Urinary System.

1. Oliguria.
The secretion of urine is slightly diminished after injection, corresponding to the increase of perspiration. I have observed this/
this diminution for example in a case where
a second dose of antitoxin was given five days
after admission to hospital, the temperature
having been down to normal for three days.
The day preceding the injection 28 oz. were
passed; the day of the injection (which was
given in the morning) the total was 15:
next day it was 25. The amount of urine
excreted at the time of an antitoxin rash
is not diminished unless there is
elevation of temperature.

2. Albuminuria.

accompanies
A transient albuminuria the appearance of
an antitoxin rash in a small percentage of
cases. Four in my series showed this: in
each it was small in amount, and was present
for two days at most.

3. Haematuria.

This I observed in one case, accompany-
ing an antitoxin eruption. The patient, a
boy of nine years, nine days after an
injection of 3000 units of antitoxin
developed a copious urticarial rash. This
came out in successive crops for two days.
On the second day of the rash albumen appeared in the urine; on the third day this was increased in amount; on the following day (the rash having now completely disappeared) the urine had a distinctly smoky tinge and chemical and microscopic examination proved the presence of blood. The next day the urine was clear and remained so as long as patient was in hospital. There was no rise of temperature or pulse rate; no back pain; and no diminution in the amount of urine passed.

4. The Diazo Reaction.

This has already been referred to (Page 62).
F. Respiratory System.

1. Asthma.

The possibility of the urticaria due to antitoxin developing on the bronchial mucous membrane has not been considered. On several occasions when a cutaneous urticaria developed in young children I have noticed a restlessness and respiratory embarrassment which seemed to indicate the presence of an actual bronchial lesion. The rapid disappearance of these symptoms simultaneously with the disappearance of the rash was a striking feature.

G. Alimentary System.

Vomiting and Diarrhoea.

These occasionally accompany antitoxin rashes. Sevestre and Martin report cases of fatal diarrhoea following the use of antitoxin, with blood in the stools. I have had no experience of these severe complications. They seem to suggest a condition of the alimentary mucous membrane similar to that found in certain eruptive fevers.

H. Nervous System.

Sedative effect.

This/
This is usually observed soon after an injection of Antitoxin. I have found it occur in the majority of cases.

Delirium.

Delirium following antitoxin is reported by Sevestre and Martin.

Tetanus.

This has occurred in this country and in Italy: but it must be regarded as purely accidental.
Prognostic Value of Antitoxin Rashes.

Whether we regard the horse serum or the antitoxic principle as the cause of antitoxin rashes their occurrence in severe cases of diphtheria must always be regarded as an indication of reaction and therefore as a hopeful sign.
IV. Enema Rashes.

Skin eruptions very frequently follow the giving or irrigation of an enema. An enema dissolves the toxic products present in the lower bowel and allows of them being absorbed into the blood. Here they act as irritants and circulating in the cutaneous vessels give rise to eruptions.

The latter are probably varied in nature: the two forms which I have most commonly observed are

(1) A Scarlatiniform rash.

(2) A Raised blotchy erythema.

(1) The Scarlatiniform rash.
This occurred in 9 of the 380 cases; it came on almost invariably within 12 hours of the injection, and was best marked about the lower part of the trunk, the buttocks and the thighs.

(2) The Raised erythema.
This occurred much more frequently, being present in 22 cases. The eruption was of a dusky red colour, and consisted of crude lumpy blotches, varying in size from that of a lentil to that of a pea. They occurred crowded together in crops; the localities most affected being the thighs, buttocks and/
and later the upper part of the trunk and, very frequently and typically, the face.

The most characteristic feature of both these eruptions is their marked asymmetry. A typical distribution is that shown in the accompanying diagram.
V. Drug Rashes.

The principle drug rashes which have to be excluded in diagnosing eruptions occurring in the course of diphtheria are those caused by the following drugs:

1. Belladonna.
This drug is often used in laryngeal cases where there is some degree of spasm. Its use may cause an eruption resembling that of scarlet fever, and as it not infrequently occurs first on the neck it may temporarily give rise to difficulties of diagnosis. The rash is however generally transient: it seldom spreads all over the body: and it often involves the face. Another fact is that itching is often complained of. No desquamation follows it.

2. Antipyrine.
This is now seldom used. The eruption it may cause is diffuse and morbilliform: it involves the face and neck, and occasionally spreads to the limbs, especially the extensor surfaces.

3. Quinine and Salicylates.
Occasionally a scarlatiniform rash follows the use of these drugs, which may have been prescribed for the throat symptoms before the diagnosis of diphtheria. It is generally confined to the face and neck.
Authorities Quoted.

11. Hutchison, Jonathan "Ophthalmic Hospital Reports": October 1859.
12. Metropolitan Asylum Board Reports.
15. Sanné "Diphtheria, Croup and Tracheotomy" Paris 1876.