THESIS

On

A Clinical Study of the action of the Toxin in severe Diphtheria in relation to Prognosis and Treatment.

By

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I N T R O D U C T I O N

After two years' experience at Plaistow Fever Hospital it has appeared to me that the full significance of the action of the toxin in Diphtheria is not recognised in its bearing on prognosis and treatment. The most dangerous stage of Diphtheria sets in after the lesion in the throat has improved or almost subsided, and this is also a feature of prognosis insufficiently emphasised in text-books.

Although the most dangerous effect of the Diphtheria toxin is its action on the circulatory system, and heart failure is the commonest cause of death, I have found from a perusal of the literature on the subject that comparatively little is written on this form of disturbance. Heart failure is described in most fever text-books but no attempt is made to explain the train of pathological changes which finally end in cardiac degeneration and death. Ker in his authoritative and comprehensive work on Infectious Diseases confines himself to a description of the pathological changes in the cardiac muscle. He makes no mention of the lowered blood-pressure which is constantly present and always precedes the first recognisable signs of heart failure; again, Dr. James Mackenzie in his classical work on "Heart Disease" (1913. P.287) writes

the following paragraph on the "Heart in Diphtheria":-

> "The complications here are so varied that danger may arise in several quarters. The heart muscle itself may be the seat of profound changes, the symptoms somewhat resembling those in Rheumatic Fever. But in Diphtheria more than in any other acute disease, there is a tendency to fatal syncope, and I do not understand how this is brought about."

Having had an opportunity of studying the different phases of circulatory disturbance in Diphtheria at Plaistow Hospital I have chosen it as a subject for my thesis, because text-books throw so little light upon it, and it is one of those issues in medicine in which the saving of life depends on a clear recognition of Pathological factors. My main object is to show that the gradual failure of the circulation which causes death in uncomplicated Diphtheria depends largely on a universal dilatation of the vessels, and that if treatment is to be effective - more particularly if better results are to be obtained than at present - the condition of the vessels must be taken into account equally with the condition of the heart.

PATHOLOGICAL CONSIDERATIONS.

It may be said that of all the Infectious Fevers the pathology, and therefore the symptomatology, of Diphtheria has been most clearly demonstrated. A number of factors combine in this disease to allow an outlook largely freed from the empiricism which attaches to medical practice in general. These factors may be tabulated as follows:

(a) The Diphtheria Bacillus was discovered in the early days of exact Bacteriology, so that there has been time for much work to be done with it by Bacteriologists, Pathologists, and Experimental Clinicians.

(b) The organism is easily isolated from cases of Diphtheria and can be readily subcultured without loss of virulence.

(c) Its specific poison is an exotoxin, freely produced, and therefore readily obtained in quantity apart from the bodies of the bacilli.

(d) The bacillus itself is pathogenic to the lower animals and so lends itself to experiment.

(e) The separated toxins when injected into animals induce toxic disturbances and pathological lesions closely resembling those occurring in man.

(f) As bearing on the last point the generalised disturbance in Diphtheria is purely toxic, since the infection is characteristically localised and superficial.

(g) This essential intoxication is non-pyrexial and excludes from the clinical picture the complex functional

disorders which are linked with raised temperature; thus the pathological consequences of the specific toxic processes are more definable.

Although it is true that pyrexia is almost always present with the development of the local lesion this has been attributed to mixed infection.

This study of Diphtheria pathology and the related symptoms covers only the general action of the toxin and not the local lesion except in so far as it is the source of an intoxication varying in degree with the case. Excluding such accidents as laryngeal obstruction, death from Diphtheria is the ultimate outcome of the specific intoxication. It must also be stated that diphtherial paralysis although undoubtedly specific and not rarely fatal is outside the scope of this inquiry. There is reason to believe that the degeneration of the peripheral nerves is caused by toxic matters which are different to those causing the ordinary disturbance of the disease.

Speaking broadly the amount of membrane formed in naso-pharyngeal Diphtheria is a measure of the severity of the general intoxication. On the clinical side this explains why the total area and thickness of the membrane form the chief basis of prognosis. The more membrane there is, the more toxin is formed and absorbed. A disturbing factor, however, is found in the varying activity of absorption. Notably, there are certain cases in which the inflammation associated with the membrane formation is of a low necrotic type with, it would seem, an excessive absorption of the specific poison and a proportionately severe general effect. Cases of this type

come under the head of toxic Diphtheria but the term is a loose one as it includes the other severe type in which absorption is not specially active but much membrane is formed and the toxin is abundant. It has been suggested that in these toxic cases with relatively little membrane but severe toxaemia, the poison is absorbed direct into the blood through rupture of the vessels. As supporting this view there is usually a blood-stained discharge from the nose and throat, which shows that the local injury is exceptionally severe and largely involves the vessels.

That absorption of toxin is the key to the severity of Diphtheria is shown by comparing the naso-pharyngeal with the laryngeal form of the disease. In all acute infections involving the fauces and naso-pharynx, and especially in Diphtheria, the comparative pathology of the local lesions shows that absorption from this area is very active. In Laryngeal Diphtheria, on the other hand, while it is frequently fatal owing to the accident of obstruction, death due to specific intoxication is rare. Such signs of marked toxic action as degeneration of the heart, kidneys, and peripheral nerves, are relatively rarer than when the lesion is faucial, even despite the fact that the membrane extends sometimes down into the air passages and is far greater in quantity. It has been suggested that absorption of toxin from the membrane in the lower respiratory tract is hindered by its extremely superficial formation. Sémon, however, has called attention to the relatively isolated condition of the larynx as regards absorption, pointing out that malignant disease in this region is exceptionally localised.

The amount of membrane present varies to such an extent in individual cases that we get all degrees of severity in attacks. From being a small spot or streak on one tonsil the membrane may cover both tonsils and extend forward over the soft and hard palates and backward over the whole naso-pharyngeal wall and along the nasal cavities. Thus Diphtheria may be so mild that no specific general symptoms are discernible. If the tonsils are partly covered with membrane there is usually definite headache and lassitude with coldness of the extremities and also a slight fall in the blood-pressure due to vasomotor relaxation. Severe sore throat is not a common complaint with patients suffering from Diphtheria. Indeed the absence of pain and discomfort in the throat is responsible for children coming late under treatment far more than any suspicion of neglect on the part of the parents or oversight by the medical adviser. A striking instance occurred recently at Plaistow Hospital: The patient, a boy, aet 6. became unwell on May 1st with what the parents thought was a bilious attack. His only symptoms were sickness and a slight discomfort in the throat which the parents took to be due to the strain of vomiting. On the following day he felt much better. But two days later as his colour was bad and he complained of headache and great lassitude a doctor was called in who on examining the throat found both tonsils completely covered with membrane which also extended on to the uvula and soft palate. There is little doubt that this patient, who succumbed on the thirteenth day of disease, could have been saved had he come under treatment early.

In very severe cases with extensive membrane the patient is usually pale and clammy to the touch, the pulse is small and rapid or abnormally slow and there is a definite fall in the blood-pressure from the universal vasomotor relaxation with the blood tending to accumulate in the splanchnic area. As all the signs and symptoms of toxaemia are here most marked this type will be kept in view during the description of the pathological changes caused by the toxins.

The toxin is taken up by the lymphatics which lead to glands behind the angle of the lower jaw. There, it inflames the glands and, if sufficiently concentrated, may produce in them changes analogous with membrane formation - due allowance being made for the diverse anatomical conditions. The bacilli are not, in large numbers at any rate, carried as far as the glands. Their presence in the glands and their distribution by the blood to distant parts of the body is to be regarded as a result of failing resistance when death is approaching.

Passing the irritated glands the toxin eventually reaches the circulation and produces its general effects, the chief of which may be classified as follows:

a. Functional relaxation of the blood-vessels.

b. Injury to the vessel walls.

c. Degeneration of the cardiac muscle.

d. Changes in the suprarenal capsules.

e. Degeneration of the kidneys with consequent albuminuria.

f. Degeneration of the peripheral nerves manifested by diphtherial paralysis.

The last "effect" as mentioned at the beginning of the thesis will not receive special consideration; it is thought to be due to a toxic matter different to that causing the general disturbance of the disease.

a. FUNCTIONAL RELAXATION OF THE BLOOD-VESSELS.

With regard to 'a' Professor Brodie has shown experimentally that the injection of Diphtheria toxin causes an immediate fall in the blood-pressure and further that this fall is rapidly antagonised by the early injection of antitoxin. This fact is borne out by examination of the blood-pressure in patients who do not receive antitoxin treatment within the first three days of the disease. At Plaistow Hospital I have found that patients admitted on the fourth or fifth day of disease have almost invariably got a low blood-pressure and that this constantly shows some rise within two hours after the injection of antitoxin. The following case is quoted as an average example:

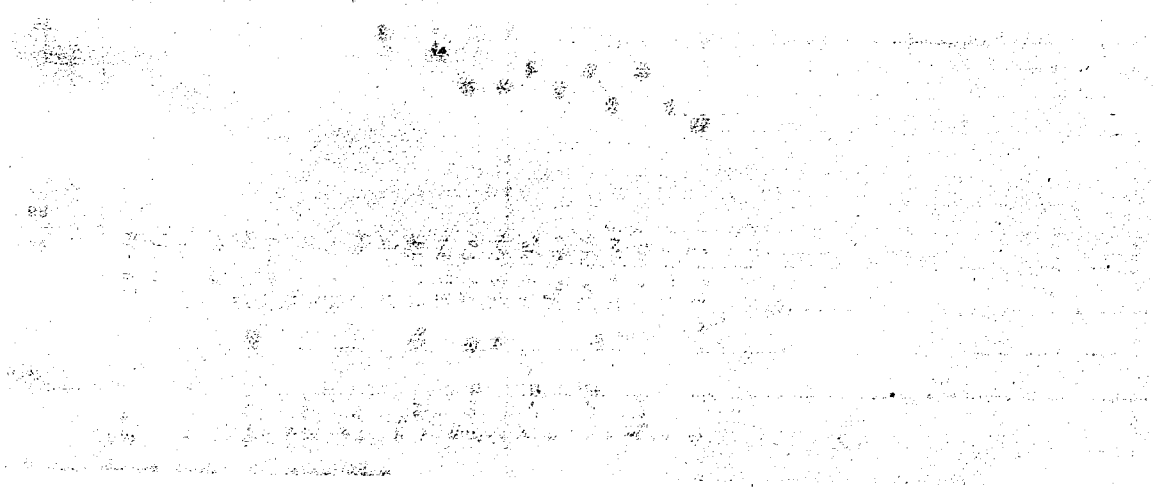
CASE.

Florence Lawrence, aged 5 years, was admitted into hospital on February 20th 1914, certified as suffering from Diphtheria. She fell ill on February 16th with vomiting and sore throat. On admission her temperature was 99.4., her pulse 128, and her respiration 28. Both tonsils and the uvula were covered with typical membrane which also extended on to the soft palate. There was profuse slightly blood-stained discharge from the nostrils and the cervical glands on both sides were considerably swollen. Her face was pale and waxy in appearance and her hands and feet were cold.

The blood-pressure in this, as in all my cases, was taken

with Riva-Rocci's sphygmomanometer, the systolic pressure as measured by the disappearance of the radial pulse being alone taken into consideration.

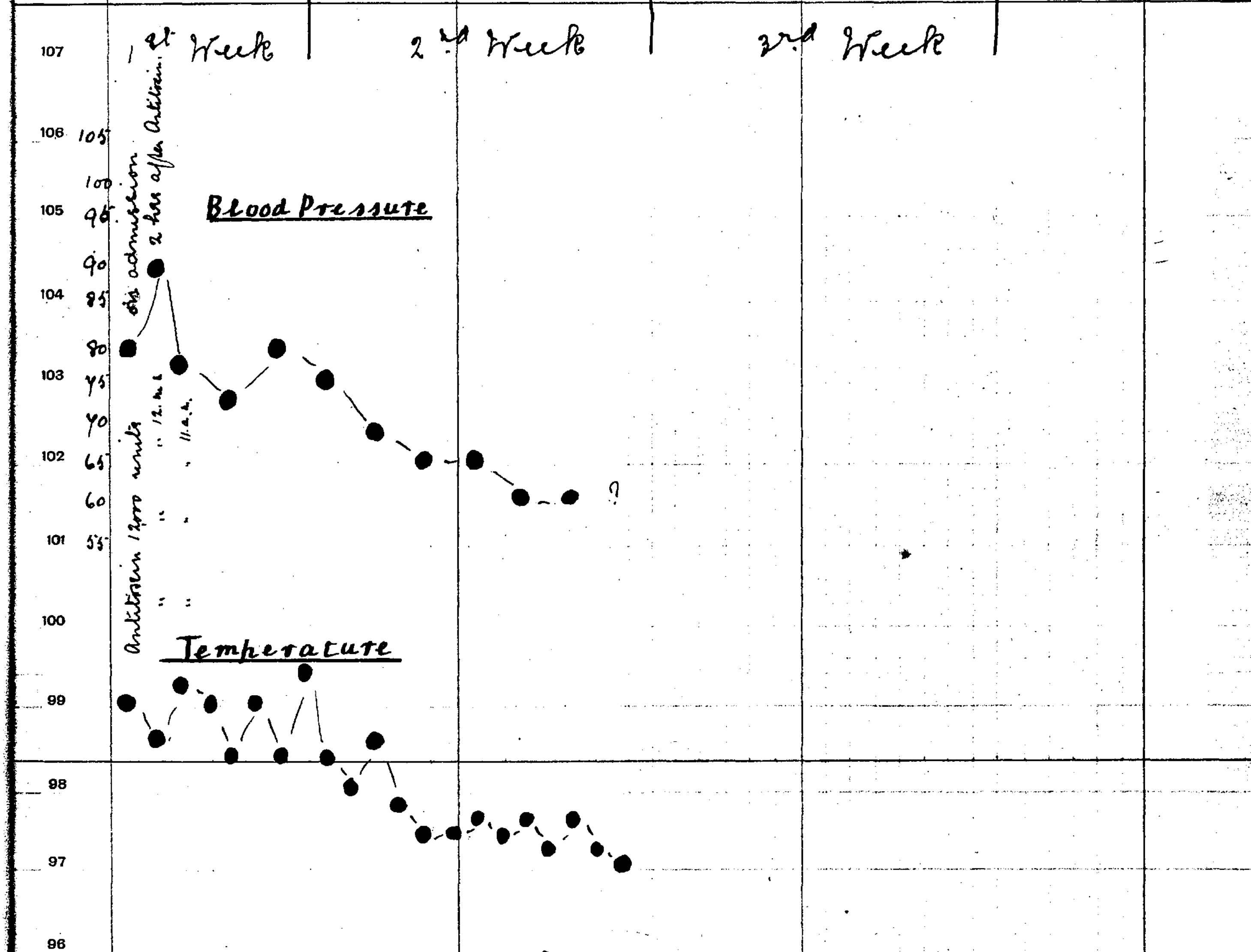
On admission the blood-pressure was found to register 80 m.m. and two hours after the injection of antitoxin it rose to to 90 m.m. By the following morning, however, it had fallen 78 m.m. and further doses of antitoxin did not appear to have any effect on it. The tracing, with the exception of a slight rise on the seventh day shows a gradual daily fall down to 60 m.m. The patient died on the afternoon of the fourteenth day of disease and on that morning it was impossible to register the blood-pressure as the pulse had disappeared at the wrist.



Name Florence Lawrence 5 yrs

1914 | DATE | 20 21 22 23 | 24 25 26 | 27 28 March 1 2 | 3 4 5 | 6 7 8 9 | 10 11 12
DAY | 4 5 6 7 | 8 9 10 | 11 12 13 14 | 15 16 17 | 18 19 20 21 | 22 23 24
TIME | M E M E M E M E | M E M E M E | M E M E M E M E | M E M E M E | M E M E M E M E | M E M E M E

1st Week | 2nd Week | 3rd Week



PULSE	128	124	124	136	124	118	122	120	104	110	98	90	80	96	96	90	96	110?	116?	?	?
RESP.	28	28	28	28	24	24	24	24	24	24	24	22	24	22	24	24	20	24	22	24	24

MOT. 19th · ⊗ ⊗ ● ● ⊗ Saline ʒx Saline ʒx

VOM. 16th I II II IIII

URINE
Q ʒ VIII. ʒ V. ʒ VIIβ+ ʒ XIV ʒ XII. ʒ II + ʒ VIII.++ ʒ X.+ ʒ VIII.+ ʒ III++ +
R Urea 144 grs 93 grs 84 grs 105 grs 98 grs
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D
A T. cloud cloud cloud cloud cloud cloud cloud cloud
B

b. INJURY TO THE VESSEL WALLS.

The considerable fall in blood-pressure which takes place during the first fortnight in severe Diphtheria is to be attributed to a general vaso-motor dilatation and there is an associated stagnation of the blood in the vessels of the splanchnic area. The toxin appears to attack the walls of the blood vessels injuring them in varying degrees according to the severity of the toxaemia. Thus in the haemorrhagic type where the toxaemia is exceptionally severe, the vessel walls are rendered so brittle that the slightest pressure ruptures them giving rise to the bruises which are the characteristic feature of Haemorrhagic Diphtheria. To a less degree do they appear to be affected in the severe form which proves fatal within the first fortnight. This has been suggested to me by the use of Adrenalin which is known to raise the blood-pressure by its direct action on the muscular wall of the arteries. I have employed adrenalin extensively in the treatment of Diphtheria at Plaistow Hospital, and have found that it raises the blood-pressure in the mild and moderate types, but shows no effect whatever on it in the severe form mentioned above.

c. DEGENERATION OF THE CARDIAC MUSCLE.

If the low blood-pressure of Diphtheria persists after the first fortnight there is reason to believe that a stage is reached when degeneration of the heart becomes an additional and finally the paramount factor in the failure of the circulation. The ventricles, especially the right, are sometimes markedly affected, so much so that from the appearance of the heart muscle, at the post-mortem, one wonders how such a state could be compatible with life. The explanation, however, is found in the dilatation of the vessels. The heart is working against such a low pressure that it is able to continue its function while its walls undergo extreme degeneration.

Much the same relation between degeneration and low blood-pressure is seen in Typhoid Fever - the other acute infection in which there is more than ordinary febrile relaxation of the blood vessels. The organ when held upwards by the large vessels may hang over the fingers (Schorstein's "mushroom" heart) Nevertheless, the degeneration of the cardiac muscle does not in Typhoid Fever reach the stage possible in Diphtheria - peripheral resistance is not reduced to the same degree.

It seems to me that a clear distinction is not made in text-books between the cases in which the cardiac muscle is directly attacked by the toxin early in the disease and those in which the heart is involved along with other parts of the body during the onset of diphtherial paralysis. Of these two classes the former in my experience is by far the more ~~fatal~~ common. During the

last two years out of 600 cases treated at Plaistow Hospital no death has occurred from involvement of the heart in diphtherial paralysis and I have only seen one case in which that organ was markedly affected at this stage, while during the same period 26 succumbed from the direct action of the toxin within the first fortnight of disease.

Taking the former class the most important factor to be reckoned with is the degeneration of the cardiac muscle. However, it appears to me that there is sufficient evidence to divide this class into two distinct types as regards clinical features. The first of these, and in my experience the commonest, is that type in which the patient lies very quietly in bed till at last life flickers out. Vomiting is not a marked feature and usually only sets in a day or two before death. Restlessness is absent and there appears to be no pain. In the second type, on the other hand, vomiting sets in early and is usually very persistent and severe. Restlessness is a marked feature, the patient tossing from side to side, unable to find ease in any position for more than a few minutes. This restlessness is sometimes accompanied by a feeling of oppression and praecordial pain; the patient giving a sudden scream.

In the former type the cardiac muscle alone is considered to be undergoing progressive degeneration while in some cases of the second it has been suggested that the vagus and possibly the cardiac plexus are affected, an assumption based on the paroxysmal character of the syncopal attacks. I have noticed that irregularity of the heart is more marked in the second type.

d. CHANGES IN THE SUPRARENAL CAPSULES.

Along with the other ductless glands the suprarenals have in recent years been receiving much attention from numerous investigators. A great deal, however, has yet to be learned with regard to the functions of these glands in health and in disease. In 1914 Oppenheim and Loeper drew attention to the great frequency of suprarenal lesions in several infectious diseases, e.g., Pneumonia, Smallpox and Diphtheria. They suggest that the acute inflammations of these organs play an important part in the production of certain morbid symptoms observed in the course of these affections, notably the neuro-muscular asthenia and arterial hypotension.

In connection with the affection of the suprarenal glands in Diphtheria, Dr J.D.Rolleston has reported that much benefit is derived by Diphtheria patients from the internal administration of Adrenalin chloride. I have used this drug in the Diphtheria wards at Plaistow Hospital, but my experience leaves me in doubt as to its value. However, the subject is one of great interest and further investigation is desirable. I shall have occasion to refer to Adrenalin again under the heading of treatment.

e. DEGENERATION OF THE KIDNEYS WITH CONSEQUENT ALBUMINURIA.

It is not surprising that the kidneys are often injured by the toxins circulating in the blood. In fatal Diphtheria they always show some degenerative change. The extent of the lesion, however, varies within wide limits in different cases. In some the kidneys may only show slight cloudy swelling, while in others there is extreme fatty degeneration. Nephritis is a very rare complication of Diphtheria. Although albuminuria is so common in severe cases blood is seldom found in the urine. The albumen usually appears in the urine towards the end of the first week; it increases in quantity during the second week, then gradually becomes less and finally disappears during convalesence.

The amount of urine excreted on the other hand bears a close relation to the level of the blood-pressure and an examination of the following charts will show that a rough parallel exists between the two. This link between the blood-pressure and urinary excretion is most strikingly illustrated in fatal cases, where the gradual drop in the blood-pressure is accompanied by a corresponding diminution in the amount of urine passed until a stage is finally reached when the urine ceases to flow. The term "anuria" is used for this condition as against "suppression" which implies obstruction either within the kidneys or in the urinary channels.

Dr. Goodall has ascribed the reduction and disappearance of the urine to nervous influences, but this is no more than an hypothesis and does not account for the close relation between the fall in blood pressure and the lessened flow of urine.

Neither can the view be held that the oliguria of Diphtheria is due to changes in the kidneys. As mentioned above the extent of the lesion found post mortem varies greatly and is slight in some anuric cases.

An interesting feature in connection with the diminished output of urine in Diphtheria is that uraemia is excessively rare in this disease. I have been unable to find any evidence of this condition from an investigation at Plaistow Hospital of two hundred cases ending in death. Instances also are rare in the literature on Diphtheria. This feature raises the question of the cause of uraemia. Our knowledge of the condition is still incomplete though many theories have been brought forward to explain the symptoms present. To my mind the condition found in Diphtheria bears out the statement made by Halliburton in his "ESSENTIALS OF CHEMICAL PHYSIOLOGY". In the section on urine he writes the following paragraph on uraemia:

> "The term was originally applied on the erroneous supposition that it is urea or some antecedent of urea that acts as the poison. There is no doubt that the poison is not any constituent of normal urine; if the kidneys of an animal are extirpated the animal dies in a few days, but there are no uraemic convulsions. In man also, if the kidneys are healthy or approximately so, and suppression of urine occurs from the simultaneous blocking of both renal arteries by clot, or of both ureters by stones, again uraemia does not follow. On the other hand, uraemia may occur even while a patient with diseased kidneys is passing a considerable amount of urine. What the poison is that is responsible for the convulsions and coma is unknown. It is doubtless some abnormal katabolic product, but whether this is produced by the diseased kidney cells, or in some other part of the body, is also unknown."

Although the course of Diphtheria is sometimes very protracted and patients may have to be kept for weeks on a

restricted diet owing to the state of the heart and kidneys, it is well known that wasting is not a feature of the disease, except as an outcome of paralysis. The explanation of this can be found in the low blood-pressure and reduced state of metabolism. Contrasted with convalescents, say in a Scarlet Fever ward, Diptheria patients always appear quiet and lacking in energy. From an estimation of the urea in severe cases I have found that the daily amount excreted continues below normal until late in convalescence.

The following two cases are quoted as showing the relation between the level of the blood-pressure and the amount of urine excreted:-

C A S E I.

On March 28th 1914, Frances Weaver, aged 10 years, was admitted to hospital suffering from a severe attack of diphtheria, both tonsils and the uvula being covered with typical membrane. Profuse nasal discharge was also present and the cervical glands on both sides were considerably enlarged. The temperature was 100.4° , the pulse 100, and the respiration 24. From the history obtained of her illness she appeared to be in the fourth day of disease.

On admission 8,000 units of antitoxin were injected, and this dose was repeated twelve hours later. On April 3rd the discharge from the nose had ceased, and the membrane was separating satisfactorily from the fauces. The pulse continued fairly regular, and no clinical evidence of cardiac degeneration could be detected.

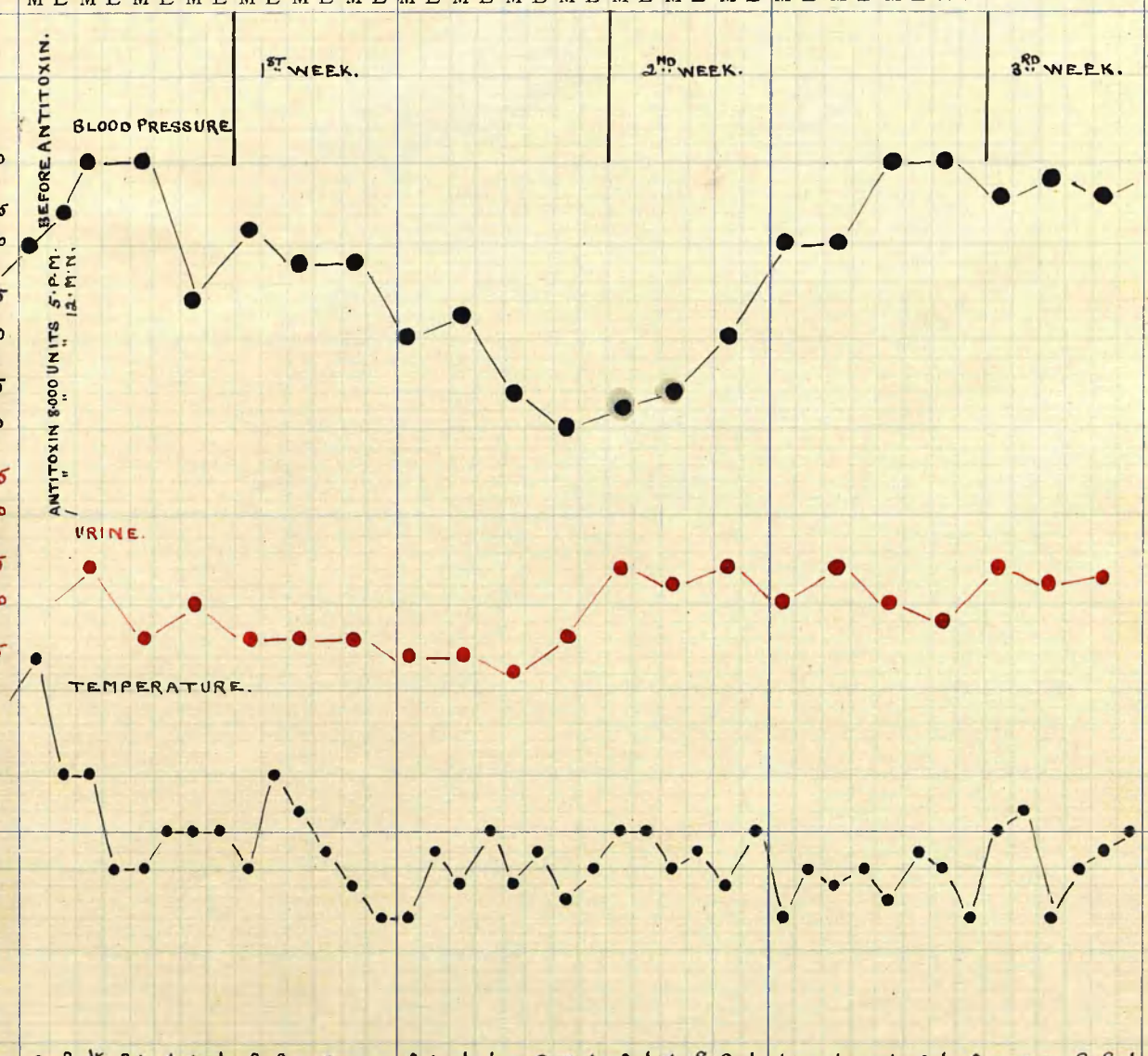
The blood pressure tracing on the chart shows a gradual fall during the first fortnight, a level of 80 m.m. being reached on the fourteenth day of the disease. After this a marked rise takes place and a higher level is maintained throughout the rest of the illness. The amount of urine passed is also marked on the chart in a red tracing and shows a rough parallel existing between the level of the blood pressure and the amount of urine excreted. The quantity of albumen in the urine, on the other hand, is found to be relatively increased when the blood pressure, and the amount of urine are about their lowest level.

This patient made a good recovery.

Name. Frances Annie Weaver 10½ yrs.

rch. April

DATE	28	29	30	31.	1	2	3	4	5	6	7	8	9	10	11	12	13	14.	15	16	17.
DAY	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24.
TIME	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E



PULSE	100	100	104	100	96	82	84	96	100	100	92	98	90	90	100	96	104	96	90	98	92	96	100	96	96	92	96	92	96	100	96	100	92	100	84	88	88	96
RESP.	24	26	26	26	26	24	24	24	24	22	22	30	30	30	30	22	30	30	30	30	22	22	30	30	30	22	22	22	22	22	30	22	30	30	30	30	30	22
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R	ACID.																			
S G	1030.																			
D	UREA. 425	388	340	288.	344	380.	210	150	98	108.	120	132.	195.	170	234	300.	171.	250	220	207.
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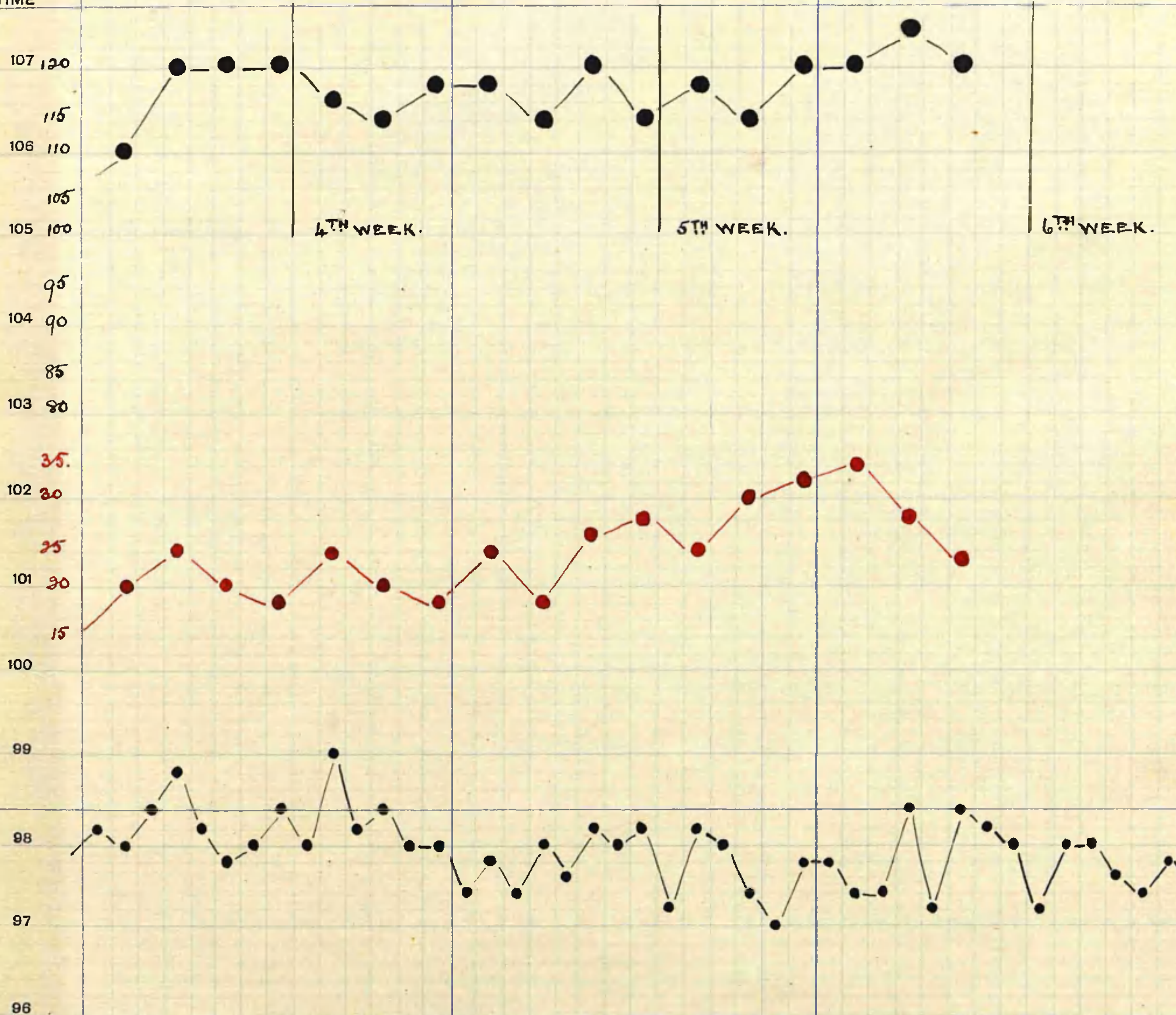
...ril.

Name: *Frances Annie Weaver.* 10½ yrs.

May.

DATE	18	19	20	21	22	23	24	25	26	27	28	29	30.	1	2	3	4	5	6	7	8
DAY	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45.
TIME	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E



PULSE	96 92	96 92	100 96	100 96	100 96	90 100	90 92	92 98	98 100	96 100	98 100	96 98	96 100	96 100	90 92	100 96	90 100	100 108	96 100	90 96	80 84
RESP.	20 20	20 22	22 22	20 20	20 22	20 20	22 24	20 20	20 22	20 20	20 22	18 20	18 18	20 20	20 20	18 18	18 18	20 20	20 20	20 22	20 20
MOT.	0	0			⊗	0	0	0	0	0		⊗		⊗		⊗		0	0	0	0
VOM.					1																
URINE Q	℥xx.	℥xxv.	℥xx	℥xviii.	℥xxv.	℥xx	℥xviii	℥xxv.	℥xix.	℥xxvi.	℥xxix.	℥xxv.	℥xxx.	℥xxxii	℥xxxv.	℥xxix.	℥xxiv.	℥	℥	℥	℥.
R																					
S G																					
D UREA	241.	200.	226.	212.	248.	232.	218.	264.													
A	T	T	T	T	T	T	T.	T	F.T.	V.F.T.	V.F.T.	N	N		N		N		N		N
B			N				N.														

C A S E II.

Emily Newman, aged three years, was admitted to hospital on February 20th, 1914. She contracted diphtheria on the 19th of February, and on admission both tonsils and the back of the pharynx were covered with typical membrane. The cervical glands were considerably enlarged on both sides; her tongue was thickly coated, and her breath foul. The face was of a mottled greyish colour, the pulse small and rapid and the extremities tending to become cold. The temperature was 98°, pulse 120, and respiration 24.

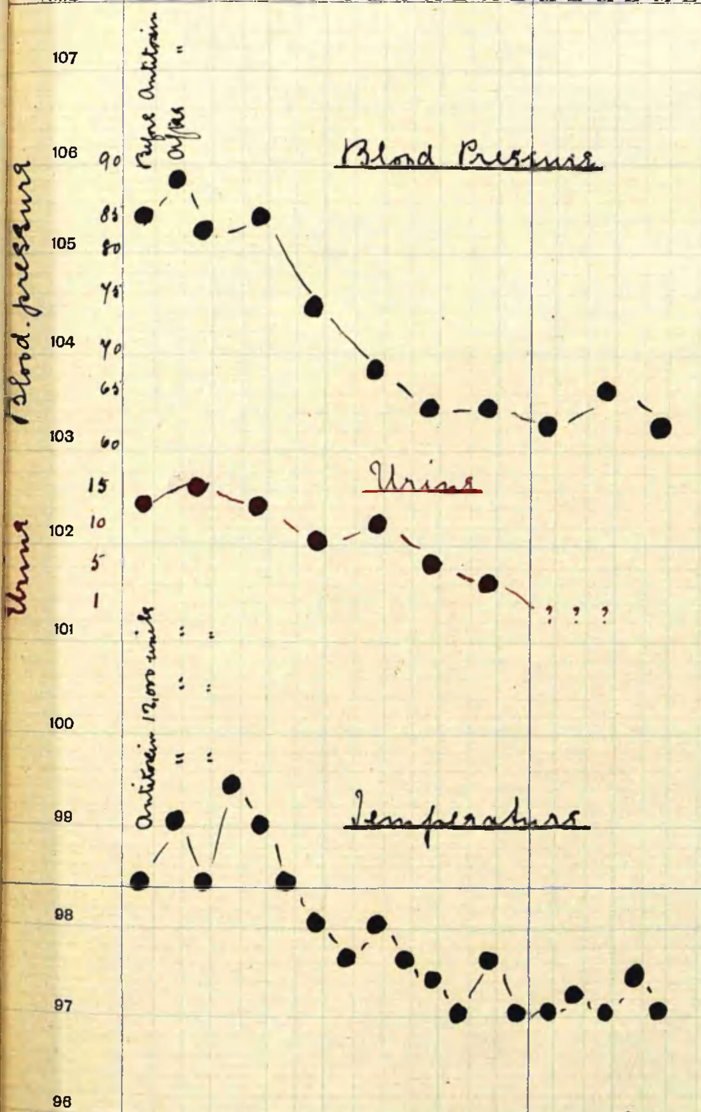
36,000 units of antitoxin, in three doses, were given within the first two days of admission. Vomiting, however, set in on the third day of disease and persisted to the end. The membrane separated satisfactorily from the fauces, the throat being quite clean by the sixth day of disease. Marked irregularity of the heart was present throughout the latter part of the illness.

The blood pressure tracing in the chart is fairly typical of fatal cases. The tracing marked in red ink denotes the daily amount of urine excreted, and is found to form a rough parallel with the level of the blood pressure. During the last two days and of the illness only small quantities of urine were passed involuntarily, the amount of which it was impossible to estimate. Marked albuminuria was present during the whole illness. The patient died on the eleventh day of disease.

Name: Emily G. Newman, 3 yrs

Feb 1914 / March

DATE	20	21	22	23	24	25	26	27	28	1
DAY	2	3	4	5	6	7	8	9	10	11
TIME	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E



PULSE	120	120	124	124	120	120	104	104	94	100	98	100	100	96	104	100	100	128?	152?
RESP.	24	26	24	24	28	26	26	26	24	24	24	24	24	24	24	30	30	30	30

	20	21	22	23	24	25	26	27	28	1
MOT.	●			⊗		⊗		⊗	●	●
VOM.										
URINE Q	13 ʒ	I ʒ	IIII ʒ	I ʒ	𝍸 ʒ	III ʒ	𝍸 II ʒ	III ʒ	IIII	
R	XI	XV	XI	VIII	IX	VI	III	+ ?	?	?
Urea grs	170.5	196	85.8	62.4	60	42	30			
S G										
D										
A										
B	T. blood	blood	blood	blood	blood	blood				

CLINICAL SIGNS AND SYMPTOMS.

From an examination of the blood-pressure in a large number of recovery cases it has been found that the fall in blood-pressure during the first week is generally slight, and that the lowest level is reached in the second week. In severe cases, however, although there may be a rise towards the end of the second week, with increasing degeneration of the heart, a further fall occurs in which relaxation of the vessels may again be a factor; such patients pass through a critical period which may last several weeks. In cases still more severe the blood-pressure is likely to fall to a level which is fatal about the tenth day or later. As extremes, patients have died in two or three days or after three weeks have passed.

Dr Biernacki has published a case of the former type, the particulars of which are as follow:

> "The patient, aged six, was admitted on the third day of disease with typical thick membrane covering both tonsils, the uvula and sides of the pharynx. There was a profuse slightly bloodstained discharge from the nose and both sides of the neck were considerably swollen. 18,000 units of antitoxin were injected a few hours after admission and this dose was repeated next day. Vomiting occurred during the first night and the patient was very restless, obtaining little sleep, but next day he was much quieter. However, on the second night vomiting became persistent, jacitation was marked and the patient could not be kept warm. He passed 4 oz. of urine that morning and ½ oz. the following morning. The pulse which had steadily weakened from the time of admission could not be counted towards the end and the sphygmometer only showed an occasional flicker. The patient was conscious until death which occurred on the second morning after admission. During the three days he was in hospital the blood-pressure fell from 95 m.m. to 60 m.m.

It is almost invariably in the second week, however, that the real amount of damage done by the Diphtheria toxin can be

gauged. By this time the local lesion has greatly improved, the membrane has completely disappeared and usually only slight traces of the remaining inflammation can be detected in the throat. The temperature now often runs a subnormal course for a time and the patient lies very quietly in bed, little interested in what goes on around him. The face is pale and sometimes of a dusky greyish hue, the expression is apathetic. The pulse may be rapid or unduly slow, but is almost invariably soft and easily compressible.

In any other fever the above signs might only suggest that the acute febrile stage was past, and the patient was entering the convalescent stage. But in Diphtheria the situation is very different. It is at this stage that the patient's life most often hangs in the balance, and the reason for this is easily recognised when we remember that, as has already been pointed out, the essential action of the Diphtheria toxin is to depress the circulation and to lead in severe cases to extreme cardiac degeneration.

As a further stage in the above clinical picture the following description will depict the conditions found during the second week in cases of severe and fatal diphtheria. The pallor becomes more marked; coldness of the extremities sets in. The pulse often remains fast, or may become unduly slow; it decreases in volume and in fatal cases gradually disappears altogether at the wrist. Vomiting, if it occurs at this stage, is an ominous sign and renders the prognosis most grave. A distressing thirst is also frequently present, the patient greedily drinking large quantities of fluid if allowed, but returning it immediately. Towards the end restlessness may

set in and the patient then tosses from side to side throwing his arms and legs about so that it is difficult to keep him warm. This may be due to a feeling of cardiac oppression which, along with vomiting, is thought by some to be caused by the early action of the toxin on the vagus. But on the other hand these symptoms are not unlike those observed to result from severe haemorrhage. And, physiologically, the patient with general dilatation of the vessels is "bleeding into the splanchnic area".

A remarkable feature of severe and fatal Diphtheria is the clear mental condition of the patient which is present to the very end. In the absence of cardiac restlessness he lies comfortably in bed, suffering no pain, and is able to recognise his relatives and talk quite sensibly. It is this condition that so easily misleads the casual observer, as he finds it difficult to realise that the patient can be dangerously ill.

If we turn now to the physical examination of a case at this stage the first outstanding feature to strike us will be the marked fall in the blood pressure. This fall is gradual but progressive and may continue for two or three days until such a low level is reached that it would have caused death if it had been sudden. But a certain degree of toleration and adjustment seems to occur which enables the patient to survive this low level. It is also favoured by the precautions now taken in the nursing of severe cases in hospital. It is still stated in text-books that death from sudden heart failure is common in Diphtheria, but I have personally never

seen an instance of this mode of death, and I understand that such a case has not occurred at Plaistow Hospital for a number of years. Modern treatment excludes sudden syncope.

In the following two cases the charts show a typical blood pressure tracing. Both patients suffered from a severe attack of Diphtheria. One died at the end of the first fortnight, the other recovered.

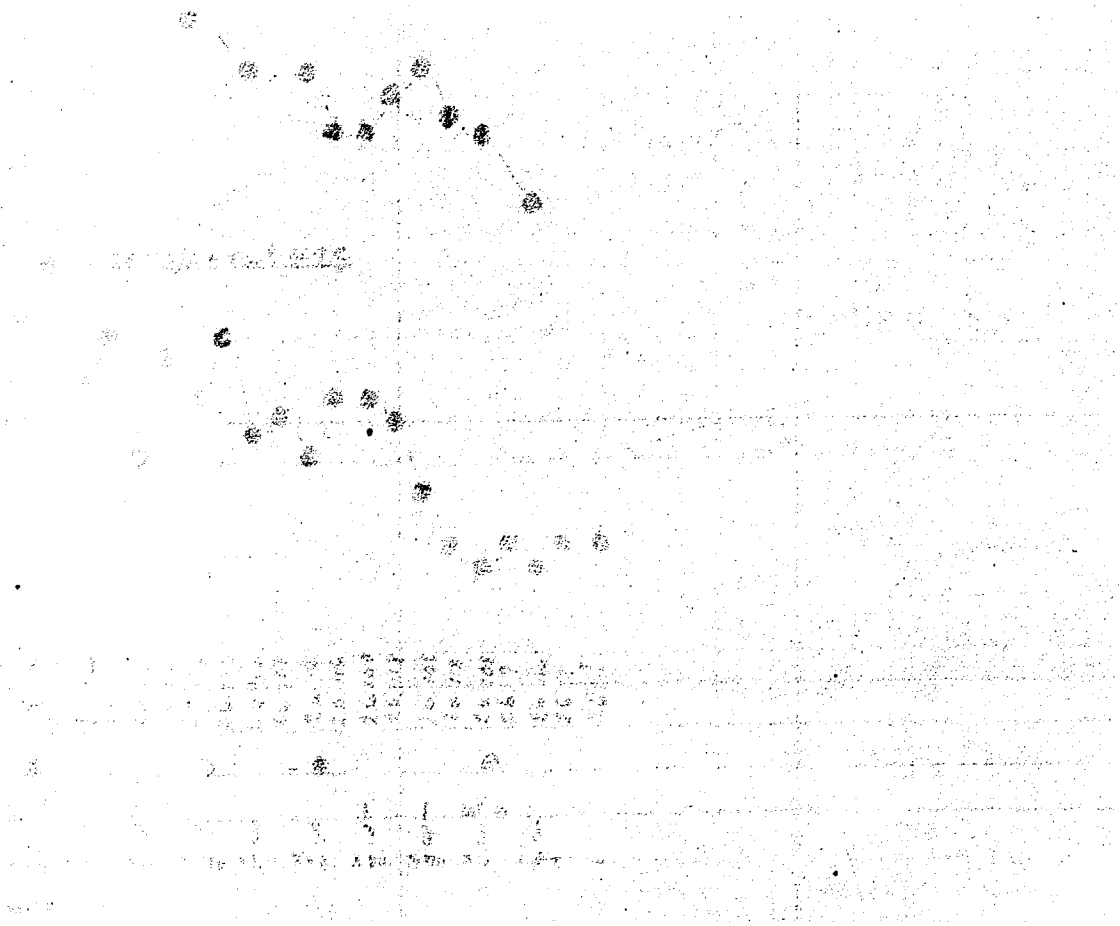
CASE 1.

William Dickie, aged 6 years, was admitted into Plaistow Hospital on May 4th, 1914 suffering from a severe attack of Diphtheria. His illness commenced on May 1st and he was therefore in the fourth day of disease when admitted. Both tonsils and the uvula were covered with thick typical membrane. The cervical glands were enlarged on both sides and the face was very pale. His temperature was 99.6°, his pulse 116, and respiration 24.

The blood-pressure on admission registered 100 m.m. and two hours after the injection of the first dose of antitoxin it had risen to 105 m.m. but after this it showed a continuous fall with one slight interruption until 60 m.m. was reached. On the last day of illness it was impossible to ascertain the blood-pressure as the pulse had disappeared at the wrist.

The membrane began to separate off from the fauces on May 7th, and two days later the throat was quite clean. The heart continued to beat regularly until the day before death. No cardiac murmur was detected throughout the illness. After the tenth day of disease, however, the heart-beats became feeble, the first sound was shortened and there was slight accentuation of the second sound over both the pulmonic and aortic areas. Intramuscular injections of 5 minims of Adrenalin chloride (1 in 1000) were given six hourly throughout the illness, but showed no appreciable effect on the circulation. Vomiting set in on the tenth day but did not become troublesome until the twelfth day when all fluids by the mouth had to be stopped.

Twenty-four hours before death the pulse had disappeared at the wrist and the extremities were cold. At this stage 1/75 gr. of strychnine was injected with the result that soon afterwards the radial reappeared but was very rapid and of small volume. The heart beats became more forcible but marked irregularity had set in and both sounds were abrupt and slapping in character. The patient died on the fourteenth day of disease.



Name. William Dickie 6 yrs.

DATE	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DAY	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
TIME	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

1st Week 2nd Week 3rd Week.

Blood-Pressure

Temperature

Antitoxin 12,000 units

PULSE	116 116 120 116 119 104 108 126 114 108 112 116 108 118 108 118 108 ? 140? ? ?
RESP.	28 24 24 20 24 24 24 26 24 24 24 20 24 26 24 24 24 26 26 26 26
MOT.	● ⊗ ● ⊗
VOM.	3rd						I				III		I							
Q	3	3	3	3	3	3	3	3	3	3	3									
R	XVIII	XXI	XVIII	XXIV	XXV	XXII	XVII	XVIII	XI.	I++										
S G	Acid																			
D	1020																			
A																				
B	V.F.T.	V.F.T.	F.T.	F.T.	T.	T.	Blood	Blood	Blood	Blood										

Name Rosie Peters 5 yrs old

April

DATE	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
DAY	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
TIME	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

1st Week | 2nd Week | 3rd Week | 4th Week

Blood pressure

107 106 105 104 103 102 101 100 99 98 97 96

115 110 105 100 95 90 85 80 75 70 65 60

In admiration 2 hrs after Antitoxin

Blood Pressure

In admiration Antitoxin 8,000 units = = 6,000 = =

Temperature

PULSE	108	100	112	120	132	126	120	124	132	120	116	124	134	116	110	112	108	104	102	108	100	100
RESP.	24	24	24	26	28	26	30	28	26	24	28	24	24	26	24	24	26	28	24	24	24	24
MOT.																						
VOM.																						

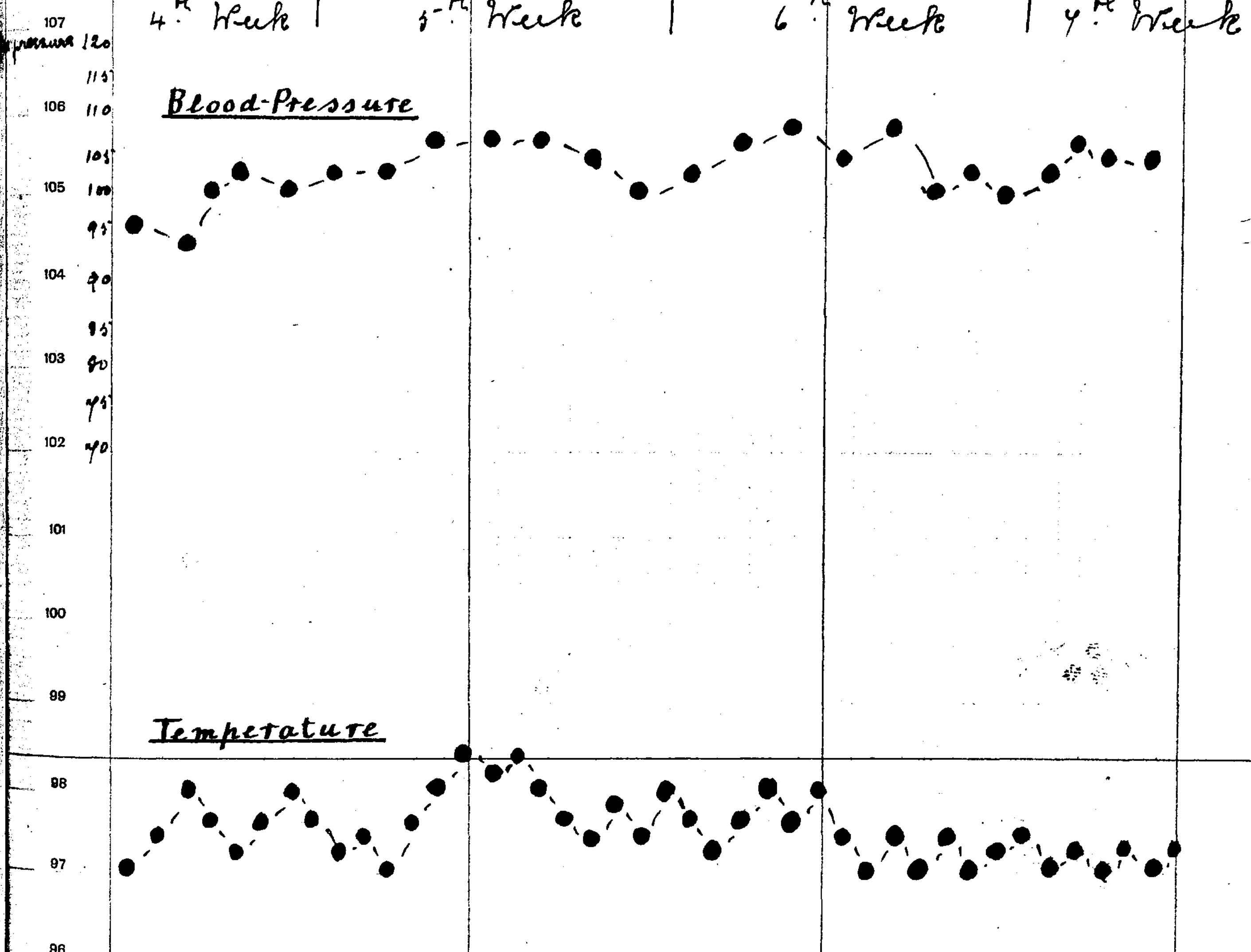
URINE																						
Q	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
R	IV.+	XXVI	XVI+	XVI	X.+	VIII	VI.	XI.+	XIII.+	XIII	XVI+	XII.	XVI.	XVII	XXIII	XXIV.	XVI+	XVIII	XX	XVIII	XVII	
S G	acid.		urea		80	92	88	63	180.	105	92	114	104	110	144	120	142	120	124	120	118	120
D	1005		gr.																			
A	blood	blood	blood		0.5	0.5	0.4	0.5	0.4	0.5	0.3	0.4	0.2	0.3	0.2	0.1	0.1½	0.1	0.2	0.1	0.¾	0.¾
B	X																					

Name Rosie Peters 5 yrs

April 28th / May

DATE	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
DAY	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
TIME	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

4th Week | 5th Week | 6th Week | 7th Week



	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
PULSE	120 118	120 116	120 120	130 124	129 132	124 120	132 126	116 122	118 126	118 124	116 120	116 120	116 122	116 128	124 128	120 130	126 126	120 118	120 132	120 124	130 124
RESP.	24 22	22 24	22 20	22 20	20 20	20 20	20 20	20 20	24 22	20 20	20 20	22 24	20 22	24 24	24 24	24 20	22 22	20 20	20 20	20 20	20
MOT.			⊗		●		⊗			⊘			⊗			⊗		●	●	●	
VOM.																					
URINE Q	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
R	XXI	XXVI	XXVII	XXIII	XXVIII	XXVI	XXXII	XXXV	XXXVIII	XXXI	XVIII+	XXIX.	XXIV	XXXV	XXXVI	XXX	XXXVI	XXXIII	XXXI	XXVI	XXXV
Urea grs.	124	130	142	150	138	146	168	180	175	194	170	175	180.	210	216	205	220	245	238	256	250
S G																					
D																					
A	T.	T.	T.	T	T.	F.T.	F.T.	F.T.	F.T.	VF.T.	VF.T.	F.T.	F.T.	VF.T.	VF.T.	VF.T.	N	N	VF.T.	N	N
B																					

So far as I know there is no other disease in which tolerance to such a low blood-pressure is found in association with a clear mind and no definite sense of suffering. The degree to which the surface of the body may be deprived of its blood supply is sometimes extraordinary. There are cases in which the patient looks as if he were made of alabaster. It is often very difficult to obtain blood from the finger point or lobe of the ear for microscopic examination. The temperature of the surface of the body is lowered, the extremities often becoming quite cold to the touch. Respiration, in the absence of lung complications, is little disturbed until death is approaching when it is likely to increase in rate and become shallow and sighing.

The following case for the particulars of which I am indebted to Dr. Biernacki will serve to show the completeness of stagnation of the lymph and blood circulation in the tissues:

> When antitoxin first came into use and it was tested at various stages of the disease at Plaistow Hospital, a child in the fourteenth day of disease received about 20.C.C. of antotoxic serum in the abdominal wall. Hardly any of it was absorbed, and on death occurring twelve hours later, some of the serum escaped on puncturing the site of injection with a scalpel.

Before proceeding to discuss the physical signs of heart failure I feel I must emphasise the fact that from the point of view of prognosis and treatment a careful note of the patient's general condition during the progress of the disease is as important as the routine examination of the state of the heart. From the description in most fever text-books one is apt to get the impression that a daily examination for signs

of cardiac degeneration is regarded as all-important for the clinician. But although it is of great importance that the heart should be carefully watched during the course of the illness, the medical attendant can often learn a great deal from the patient's colour, pulse, blood-pressure and urine. It not infrequently happens in fatal cases that no sign of cardiac degeneration can be detected by auscultation until a day or two before death, while the patient's general condition will readily warn the physician of the gravity of the case.

However, when the heart shows evidence of failing, this at once becomes the paramount factor in the case. The first sound gradually becomes shortened until at last it resembles the second sound. If a mitral murmur appears it is always systolic and conduction into the axilla is slight or absent. In the pulmonic area there may be marked accentuation of the second sound and reduplication is present in the majority of cases. If a murmur is detected in this area it is of the haemic type. With the onset of dilatation of the left ventricle the apex impulse becomes more or less diffuse and is easy to ascertain in marked cases. Some dilatation of the right ventricle may also be detected. Irregularity of the heart may now set in and is always of grave significance. Aortic murmurs have not occurred in my experience. The outstanding sign of degeneration in this area is accentuation of the second sound. This accentuation is far more significant than that in the pulmonic area.

Aortic accentuation as a sign of degeneration was first discovered by Dr. D.B.Lees when studying the cause of sudden

death after Diphtheria, Typhoid and Influenza in certain cases. The discoverer put forward the curious view that as the superficial vessels were relaxed, there must be constriction in the splanchnic area causing increased pressure in the aorta. This suggestion was immediately criticised and proved to be wrong. In the first place, the surface of the body in cases of aortic accentuation during the acute stage of Diphtheria has a diminished blood supply - a condition only compatible with splanchnic relaxation. Also it is impossible that the superficial blood-pressure should be low and the internal blood-pressure high. Inevitably, in a system of tubes supplied in common by a main trunk, the pressure must equalise itself. The accepted explanation of aortic accentuation is that the mechanical conditions under which the aortic valve closes are altered. Normally, on the systole of the left ventricle there is a moment when it remains contracted, supporting the blood in the aorta in a relative state of quiescence. At this time a swirl of blood occurs at the beginning of the aorta and causes the valve cusps to float together. When the valve is closed the ventricle begins to relax and what is heard as the second sound is the sudden tensioning of the cusps - a sound comparable with that produced when a paper bag, being blown into, suddenly reaches its maximum inflation.

In acute degeneration of the heart the systole as shown by the first sound is shortened. This shortening no doubt extends to the pause at the end. Also diastole is more rapid. Given these conditions it is not necessary to have increased pressure in the aorta in order to produce an unduly sudden and forcible closure and tension of the cusps. The explanation,

in fact, is found in the difference between the pressure in the aorta and in the ventricle at a given point in the cardiac cycle. The value of aortic accentuation is greatly enhanced by the fact that it is frequently present as a sign of degeneration when dilatation has not occurred or has disappeared.

[illegible] ...ever is the degree of intoxication.

[illegible] ...In many mild cases the tonsils are only part... ...with membrane. With appropriate treatment they ...ely to recover and usually escape paralysis. ...urin is rare.

[illegible] ...In this class are cases in which both tonsils ...ely covered with membrane. A definite fall in ... ...becomes, often with albuminuria. Some degenera... ...heart may develop, and slight paralysis sometime... ...death is unusual.

[illegible] ...These are cases in which the membrane invades ... ...of the soft palate. They are always severe and ... ...he sequence of symptoms already traced is common.

[illegible] ...Finally there are cases in which the soft pal... ...covered ... ...

P R O G N O S I S.

In faucial Diphtheria there are two outstanding factors which enable the physician to form a prognosis with unusual certainty. These factors are:

a. The amount of membrane present.

b. The day of disease on which antitoxin treatment is begun

With regard to the amount of membrane the cases can be divided roughly into four classes - due allowance, however, being made for age susceptibility since the younger a child, the greater is the degree of intoxication.

1. In many mild cases the tonsils are only partially covered with membrane. With appropriate treatment these are likely to recover and usually escape paralysis. Also albuminuria is rare.

2. In this class are cases in which both tonsils are completely covered with membrane. A definite fall in blood-pressure, occurs, often with albuminuria. Some degeneration of the heart may develop, and slight paralysis sometimes ensues. Death is unusual.

3. These are cases in which the membrane invades a portion of the soft palate. They are always severe and death after the sequence of symptoms already traced is common.

4. Finally there are cases in which the soft palate is largely affected and even the hard palate may be involved. The mortality in such cases is high; if they survive the slow failure of the circulation peculiarto the disease, the chance is large that they will have severe and possibly fatal paralysis.

It must be added that involvement of the pharynx and the nose, according to the degree, proportionately increases the gravity of a faucial case.

The day of disease on which antitoxin is injected is of the greatest importance in prognosis. The earlier this treatment is started the better are the results obtained. It is very rare for a patient receiving an adequate dose of serum on the first day to succumb but with each succeeding day the death-rate rises, and for cases injected for the first time after a week has elapsed, it not infrequently is above 20 per cent.

The severe toxic and septic cases are most liable to failure of the circulation, which usually sets in after the throat symptons have cleared up. Haemorrhagic cases showing the small typical haemorrhagic spots under the skin and bruising at the site of injection are almost invariably fatal.

Late vomiting has the gravest significance. Once it has become established it shows a definite tendency to persist until death, and is itself a factor in the failure of the circulation. It sometimes persists even when administration of food and water by the mouth is stopped, the patient ejecting small quantities of mucus, which occasionally contains altered blood.

The prognosis in paralysis is good as long as the respiratory muscles are not involved.

SPECIFIC TREATMENT

A study of the effect of antitoxin elicits facts which do not seem to accord with the fixation of toxin as required by Erlich's side chain theory. Clinically, in early but toxic cases, the sphygmometer often shows a rapid rise in blood-pressure after antitoxin has been injected. Assuming that the toxin does not act without becoming fixed in the living tissues, it is difficult to understand how the antitoxin neutralises it. The assertion that the antitoxin can withdraw the toxin from the tissues owing to its mass and greater affinity is no more than an hypothesis.

Nevertheless, the pathological and clinical facts strongly suggest that the toxin does eventually become fixed in the tissues with later results which may extend to many weeks. It is in keeping with this apparent process that, after a few days, the utility of antitoxin is very doubtful. As regards the massive action of antitoxin in releasing toxin from the tissues, again it is significant that the heroic doses of serum in vogue a few years ago are no longer used. In this country there is a tendency to limit the maximum dose to eight thousand units, repeated at intervals of eight or twelve hours, twice or thrice, according to the progress of the local lesion. On the other hand, not to obtain a massive action on fixed toxin but on the general principle of neutralising it, it is becoming the practice abroad to give at the earliest possible moment a single maximum dose which may exceed twenty thousand units.

A N A P H Y L A X I S

During the last two or three years the attention of clinicians has been directed to anaphylaxis as a danger in serum treatment of all kinds and particularly in Diphtheria since it is so regularly treated. It is generally stated, and was laid down by Dr. Goodall at the Royal Society of Medicine, that anaphylaxis is aggravated serum sickness per se. The serum rash appears earlier and is often unduly intense, while other phases of the serum sickness are also very marked and may be accompanied by extreme cardiac depression. Certain effects produced by serum when injected intravenously, however, as described later, strongly suggest that the disturbance is due partly to serum sickness proper, which, in non-anaphylactic cases ordinarily develops after several days' incubation, and partly to the accentuation of the direct toxic effect of horse serum which is always immediate.

It has seemed to me in severe cases of anaphylaxis that both these forms of disturbance are traceable. Indeed this is true of Dr. Goodall's description of anaphylactic phenomena. At one time all the cases of Scarlet Fever going to the Plaistow Hospital Convalescent Home received a prophylactic dose of antidiphtheritic serum and some of these afterwards contracted Diphtheria for which a further dose was given. I have, therefore, had an opportunity of studying the incidence and severity of anaphylaxis. My opinion so formed is that the anaphylactic state is by no means constantly present at any rate in a clinical sense, and that its danger has

been exaggerated. The latter point is important, as fear of serious disturbance may prevent clinicians from administering serum when it is urgently required. I do not suggest that serum should be given intravenously where there is a possibility of anaphylaxis, but I would not hesitate to inject it subcutaneously in any case where antitoxin was ordinarily indicated. If there is any reason to fear the effect of serum treatment it is always possible to obtain a highly concentrated preparation so that the dose of horse serum is greatly reduced.

INJECTION OF ANTITOXIN.

As to the methods of administering antitoxin, no beneficial result has been observed at Plaistow Hospital from giving it by the mouth and rectum. Three other methods require notice, namely:

1. Intravenous injection.
2. Intramuscular injection.
3. Subcutaneous injection.

In this country the intravenous route was first advocated by Dr. D.L.Cairns who published a favourable report of this method in 1902. Following him, Biernacki and Muir published an account of forty-five cases so treated, in two series. Their conclusions were very conservative, but on the whole suggested that the method had some value as against other modes of administration. Abroad the treatment of a small number of cases was reported by Gagoni, Zamboni and Mongour. Meanwhile Cruveilhier, testing the effect of antitoxic serum by the injection of toxin into guinea-pigs, found that six hours were gained by the intravenous as against the subcutaneous method. The former method was still beneficial two hours after the latter had ceased to be so. He also asserted that the venous route was the best for antitoxin and that it assured a maximum effect. Bisson, working at Plaistow Hospital, has published the largest number of cases, namely two hundred. A striking fact brought out by him is the marked average difference existing in the direct toxic effect of commercial

anti-diphtheritic serums - an effect no doubt due to the amount of care taken in the obtaining and breeding of horses whose blood serum has a low toxicity. Bisson mainly worked with two serums, one showing a maximum and the other a minimum toxicity. The chief toxic symptoms were a rapid rise in temperature often accompanied by rigors, stupor, and marked circulatory depression lasting some hours. No patient died from this disturbance, although in some instances it was severe. The death rate in Bisson's cases is 16.5 per cent, but as they were mainly selected for their severity out of 660 cases, this outcome was not regarded as unfavourable to the method. The dose varied according to the severity of the case from 10,000 to 30,000 units. This was sometimes repeated, or a second dose given subcutaneously.

The intravenous method is not much used at the present time. One great disadvantage to its routine employment is the difficulty often met with in picking out the veins, especially in young children.

The intramuscular injection of antitoxin has only recently come to the front and very little information as to its value is obtainable. I have been using this method lately at Plaistow Hospital and the results so far have been satisfactory. The site chosen for the injection is the outer region of the thigh. There is no danger of injuring any important structures in this area, and a dose of 8,000 units can be injected quite easily. The pain on injection does not appear to be so acute as in some other parts of the body. The advantages of this method are that the operation is easily performed and a more rapid effect of the antitoxin is obtained. It is also comparatively

painless, and local reaction appears to be less frequent than with the subcutaneous method.

Subcutaneous injection is still most widely used in fever hospitals and general practice in this country. The site chosen is the abdominal wall, in the loose areolar tissue. Its advantages are:

1. A large quantity of serum can be easily given.
2. Owing to the looseness of the tissues, the pain is relatively slight and only transient.
3. Where a local reaction occurs with tenderness and pain, owing to the position of the body there is no pressure on the part.
4. In the rare event of an abscess forming, its position does not inconvenience the patient as he lies in bed. Now and then when large doses of antitoxin are given even subcutaneously, the immediate toxic effects already described are observed in a modified form.

CLINICAL TREATMENT.

The dieting of Diphtheria patients from the standpoint of wasting is not so important as in other fevers running a prolonged course. It is, however, a weighty issue as regards the giving of fluids since a deficiency of water tends to produce a fall in blood-pressure. This is shown by the reverse fact that a marked rise in blood-pressure is observed in various fevers when a saline infusion is given. The administration of water is also extremely important in relation to the output of urine, even apart from the level of the blood-pressure. The aqueous constituent of the urine must be supplied or renal excretion is hampered.

Patients frequently vomit in the initial stage of the disease. This disturbance is not dangerous as it passes off when solid food is replaced by a liquid diet. The outlook in regard to late vomiting, however, is very different. Its bearing on prognosis has already been mentioned. In practice the physician has to keep in mind the readiness with which such vomiting is determined by food and drugs. As the blood-pressure sinks below 80 m.m. special attention must be given to diet. If vomiting occurs, the patient should at once be put on some such preparation as peptonised milk or peptonised whey. At this stage and even before vomiting has occurred all drugs should be suspended, including aperients, the bowels being relieved by enemata. These precautions are necessary because while "late vomiting" is easily induced by the agents

mentioned it is thereafter likely to persist in spite of all treatment until death occurs. Even when every care is taken it is certain to supervene in a large proportion of the severe cases, and its effective treatment is at present one of the chief questions in fever practice. Many lives would be saved if vomiting could be stopped with any certainty. This is shown by the recovery of some cases which seem to respond to treatment. At Plaistow Hospital, oxygen is given for ten minutes every hour when vomiting occurs. The latter is likely to be lessened and now and again is stopped.

Several clinicians have independently called attention to the value of atropine in severe Diphtheria. The drug, however, has not been used extensively enough to establish its usefulness. At Plaistow Hospital sulphate of hyoscyamine, gr. $\frac{1}{300}$, 6-hourly, was tried, but the results were disappointing.

Since attention has been called to the changes in the suprarenal glands in Diphtheria, adrenalin has been employed not merely for the vomiting but early in the disease. One object has been to counteract the vaso-motor relaxation. It may be said, however, that a great deal has still to be learned regarding the physiological action of adrenalin. Dr. Allan Watson has reported that from experiments on three healthy male subjects, he found that the effect of adrenalin was to decrease the diastolic blood-pressure more than it raised the systolic. He suggests that one of the physiological actions of adrenalin in man might be to dilate the aortic orifice and produce a temporary regurgitation.

Assuming, as is now generally held, that the blood-pressure represents a balance between the suprarenal, thyroid, and

pituitary secretions, it may well be that the maintenance of higher blood-pressure under various conditions will present difficulties at present unforeseen. On the other hand, Dr. J.D. Rolleston states that from the use of adrenalin in Diphtheria benefit may accrue which cannot be measured by a rise in blood-pressure. Adrenalin has been prescribed in a considerable number of cases at Plaistow Hospital and I am unable to say that the results are decidedly favourable. In the fatal cases it did not appear to have any effect on the blood-pressure while in those that recovered it was difficult to judge how much benefit was derived from the adrenalin. The drug was given intramuscularly, the dose being 5 minims 6 hourly of the 1 in 1,000 solution of adrenalin chloride. No toxic effects were detected even in cases where this treatment was continued for a week.

The following two cases, with charts, are quoted as average examples of the cases treated. One of these died on the fifteenth day of disease; the other recovered.

C A S E 1.

Margaret Speckernell, 3 years old, was admitted to hospital on February 7th 1914, suffering from Diphtheria. The illness began with an attack of vomiting on February 3rd, slight sore throat was also complained of, but the true nature of the complaint was not diagnosed until four days later.

On admission, both tonsils were covered with membrane, and the glands on each side of the neck were swollen. There was profuse discharge from the nostrils. The temperature was 100° pulse 132, and respirations 28.

Within the first two days of admission 28,000 units of antitoxin were injected. On February 9th the temperature dropped down to normal, the pulse became slower, but was very compressible; no cardiac murmur or irregularity was detected. The nasal discharge had now cleared up, and the membrane was beginning to separate off the tonsils. By February 11th the throat was quite clean. The patient had vomited twice on the day of admission and four times on the following day, but during the next two days she was able to take and retain a fair quantity of fluids. Vomiting, however, set in again on Feb. 11th and gradually became worse, persisting until the end even although all food by the mouth had been stopped three days before death. The pulse was slow and very compressible, but on the last day it became rapid and very irregular.

The blood-pressure on admission registered 86 m.m. and rose to 90 m.m. two hours after the first injection of anti-

toxin, but after this it fell steadily until 60 m.m. was registered, twelve hours before death. On the day after admission 5 minims of adrenalin were administered every four hours for three days, and then it was given six hourly for other four days. It did not appear to have any effect on the blood-pressure.

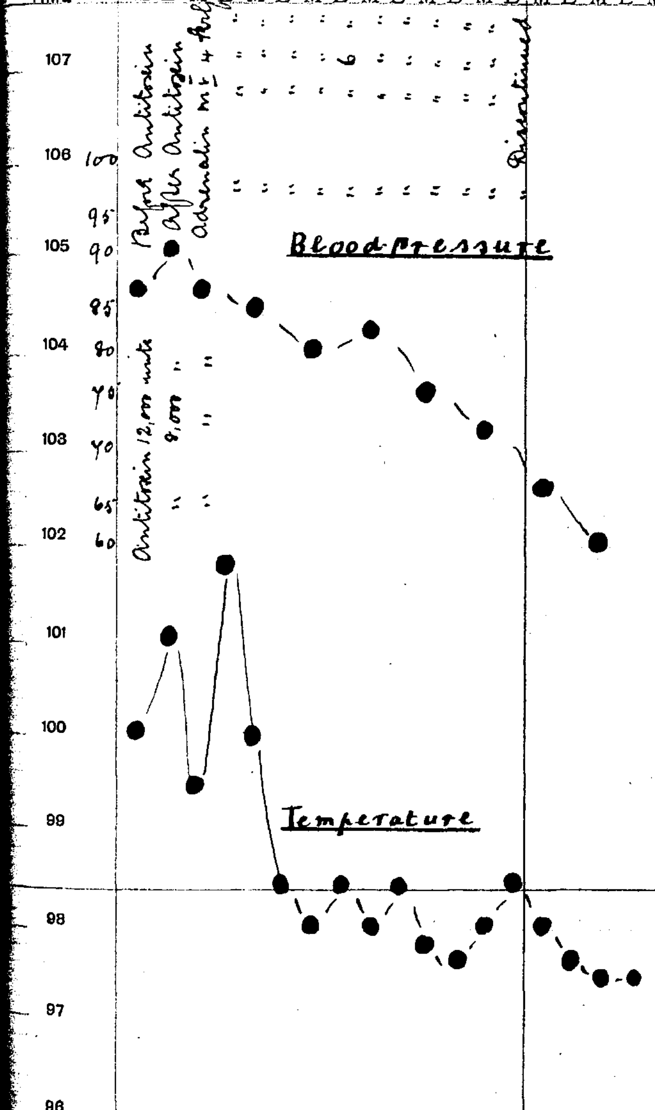
The patient died on the twelfth day of disease.

Name Marg: Spickernell 3 yrs

Ly H 1914

DATE	7	8	9	10	11	12	13	14	15
DAY	4	5	6	7	8	9	10	11	12

TIME: M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E



PULSE	132	144	128	120	88	88	88	88	84	92	76	72	68	64	72	60	110	136?
RESP.	28	30	30	30	24	20	20	20	20	20	20	20	20	20	36	44	48	48

MOT.	⊗			⊕			⊗		●
VOM.	II	IIII			II	IIII	~~IIII~~ III	~~IIII~~ ~~IIII~~ I	~~IIII~~ ~~IIII~~
	3	3	3	3	3	3	3	3	3
URINE Q	+	VII.	VIII +	X.	XIII + VIII	IV.	+?	+?	
R									
S G									
D									
A									
B	Blood	Blood	Blood	Blood	Blood	Blood			

C A S E 2.

On the 12th of March 1914, Ada Morley aged 7 years, was admitted to hospital suffering from Diphtheria. Both tonsils were completely covered with membrane, also a small portion of the soft palate, and there was profuse discharge from the nose. The cervical glands were enlarged on both sides. She was in the second day of disease when admitted; the temperature was 100°, pulse 120 and respirations 26.

The blood-pressure on admission registered 100 m.m., rising to 105 m.m. two hours after the first injection of antitoxin. She received 24,000 units of antitoxin on the day of admission and 12,000 units on the following day. The membrane began to separate off the tonsils on March 15th and three days later the throat was quite clean.

The general trend of the blood-pressure during the first ten days was in a downward direction, reaching 80 m.m. on the twelfth day of disease. On the eleventh day the administration of 5 minims of adrenalin every six hours, was begun and continued for a week. During this time the blood-pressure tracing showed a steady rise, a level of 100 m.m. being reached in four days and this was more or less maintained during the rest of the illness.

It is difficult to judge how much, if any, of this improvement was due to the adrenalin. Recovery cases usually show a slight rise in the blood-pressure about the end of the second week, though it may not be so marked as in the present case. The patient suffered from paralysis of the soft palate during the fifth week of disease, but ultimately made a good recovery.

March. Name. Ada Moorley. 7 yrs. April.

DATE	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31.	1
DAY	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22.
TIME	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E	M E

1ST WEEK. 2ND WEEK. 3RD WEEK.

BLOOD PRESSURE.

TEMPERATURE.

ON ADMISSION. ANTITOXIN 12.000 UNITS GIVEN 5 P.M.
2 HRS AFTER ANTITOXIN. 11.30 P.M. " " " 11.30 A.M.

ADREN. M.V. 6 HRLY.

ADREN DISCONTINUED.

PULSE	120	112	116	108	116	108	112	104	96	104	100	100	104	100	92	96	92	96	96	80	92
	100	96	92	96	96	92	88	96	96	100	96	92	88	96	96	104	108	100	92	96	96
RESP.	26	26	26	28	28	24	24	26	24	24	24	24	24	22	22	22	24	24	24	24	24
	22	22	22	22	22	24	24	24	22	22	22	22	20	20	22	22	22	20	22	22	22
	20	22	22	20	22	22	20	22	22	24	24	24	24	24	24	24	24	24	24	24	24
	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
MOT.	10 hr	⊗	0		0	0	0	⊗		⊗		⊗			⊗		⊗		⊗		⊗.
VOM.		1																			

URINE

Q		℥xii.	℥xviii.	℥xxii.	℥xix.	℥xviii.	℥xv.	℥xvii.	℥xix.	℥xvi.	℥xiii.	℥x.	℥x.	℥xv.	℥xvii.	℥xxii.	℥xxvi.	℥xix.	℥xviii.	℥xii.	℥xvi.
R		ACID																			
S G		1025.																			
D	UREA. GRS.	240	240	296	198	184		204	171	160	130	110	120	90	132	125	136	144	153	130.	
A		T.	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
B		N.			N			N				N			N				N.		

If adrenalin could produce a marked and persisting rise in blood-pressure in advanced cases with a degenerated and dilated heart, and perhaps vomiting, it might endanger life. Using one of the most powerful vaso-constrictors known, namely barium chloride, some years ago to raise the blood-pressure under such conditions, Dr. Biernacki observed a very temporary improvement followed by collapse and death. It stands to reason that the blood-pressure cannot be safely raised when the heart is already dilated, and even overtaxed by the lower pressure.

Reverting to late vomiting I am not satisfied that adrenalin is a preventive. It has been combined with atropine by Coghlan who also includes strychnine in his prescription, a drug which has no reputation in the treatment of late vomiting, and if anything tends to make it worse. A clinician, in dealing with late vomiting accompanied by cardiac degeneration and dilatation, is in a difficult position. The patient is dying from a fall in blood-pressure which cannot be raised with safety.

It is plain that drugs, to be safe, should stimulate the cardiac muscle without materially raising the blood-pressure by vaso-constriction. The most valuable drug of this class is alcohol when used in sufficient but not excessive doses. It must not be given too diluted or the stimulating effect is lost. Thus it is better to prescribe an adequate dose at longer intervals than to use smaller doses more frequently or to dilute the alcohol by mixing it with fluid diet and giving it more or less continuously. For a child

of four years, one and a half ounces of whisky or brandy in the 24 hours is the usual amount prescribed and is given in two-drachm doses.

Next in value to alcohol is camphor. It is usually injected hypodermically in the form of Curschmann's solution in olive oil. Owing to the presence of the oil the absorption of the camphor is retarded and regulated. Thus a continuous effect is obtained and the chance of toxic symptoms lessened. The same principle has been adopted in the hypodermic treatment of syphilis by mercurial drugs with a fatty substance. The clinical rule is to begin with alcohol and to use camphor as an additional stimulant when the patient's condition becomes critical.

The value of strychnine, in the condition under consideration, is not so certain as text-books imply. In some cases the pulse is steadied and its tension improved, at any rate for a time; but, as has been already noted, increased tension may be dangerous. It is therefore significant, as has been pointed out by Ker, that when strychnine is withdrawn in the treatment of febrile heart failure an improvement in the pulse is sometimes noted. At Plaistow Hospital strychnine is only prescribed in minimal doses and its effect carefully watched. From observations at this hospital the conclusion has been arrived at that the indiscriminate use of strychnine in grave fever cases - a feature of general practice - must be dangerous. For a child of 4 years, in the Plaistow Hospital wards, $\frac{1}{175}$ gr. is the maximum dose, given six or eight hourly and rarely continued for more than two days.

Apart from the use of drugs, efficient circulation in the vital centres can best be maintained by tipping up the lower end of the bed, and this practice has become universal for cases with a dangerously low blood-pressure. That it is effective is proved by the fact that, occasionally, when the lower end of the bed is dropped, the condition of the pulse becomes worse. Also, long before there is danger of circulatory weakness - indeed in all cases in which it can be foreseen - the patient from the first lies in bed without a pillow, to keep the head low. Children who cannot otherwise be prevented from sitting up wear a belt which allows them to move freely but not raise themselves.

Experience has shown that it is very important to keep the surface of the body and the extremities warm. It is not sufficient to heap clothing on the patient. Hot water bottles have to be placed in the bed and sometimes blankets warmed before a fire are wrapped round a patient.

Oxygen inhalation has a very definite value, no doubt because it maintains tissue respiration in the vital centres. Its use should not be postponed too long. Too often the ordering of oxygen implies that the patient is in extremis.

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