T H E S I S.

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A Clinical Study of the action of Diphtheria toxin in relation to paralytic phenomena.

CONTENTS.

INTRODUCTION.

The subject of Paralysis occurring in the course of Diphtheria has always attracted considerable attention and although must haw been written on it, our knowledge cannot be said to have advanced materially since the work of Bretonneau at Tours in the beginning of the 19th century.

It is still a mystery why some patient develop paralysis during or after an attack of diphtheria whilst others do not. Thus Rolleston (1) in his careful study of 2,300 cases mentions 216 very severe, of whom only 70.8% developed paralysis while, on the other hand, 23 out of 890 mild cases showed some sign of nerve involvement.

The fact that paralysis can be produced experimentally in animals does not help us greatly in the elucidation of the nature of the condition. Presumably there is absorption of toxin in all cases of diphtheria and yet only 15-20% may develop paralysis. In the following series of over 1100 cases the figure is 16.2%.

The work of Dêjerine, Vincent, Meyer and Sidney Martin seems to prove that the lesion is a true neuritis produced by the diphtheria toxin. Under what circumstances does such neuritis/

neuritis develop? Why does it pick out certain nerves in preference to others? Why may paralysis come on after a mild attack whilst it is sometimes absent after a severe one?

These and other points are in need of elucidation and it is the writer's object in this thesis to give an account of his experience of the condition in a series of cases which came under his care at Plaistow Fever Hospital.

With regard to the fatal cases, it will be shown later that the great majority of deaths occur during the first fortnight of the disease, only a small number occurring during the later weeks. If, therefore, the patient can be tided over the fateful second week there is good hope of his ultimate recovery even if he develop a severe attack of paralysis.

Opinions still differ as to the explanation of cardiac failure during the first fortnight some believing that it is nervous in origin, others ascribing it to toxaemia affecting directly the endothelium of the peripheral vessels and the heart muscle itself.

Biernacki (2) in 1899 pointed out that the symptoms in uncomplicated fatal diphtheria are sufficiently constant to justify a general description. These he describes as pallor, coldness of the surface of the body, progressive weakness/

weakness and irregularity of the pulse, oliguria leading to suppression, frequently oppressive cardiac pain, sickness and jactitation. The writer's experience at Plaistow Hospital bears out this observation and it is to the above syndrome that the term "cardio-vascular paralysis" is applied in the thesis.

The symptoms mentioned above may be present for a few days before a fatal result ensues, but frequently the change in the patient's condition may take place with dramatic suddenness, the onset of vomiting being the herald of what is almost certain death in 24 hours. In one case in the series investigated, the fatal termination followed 12 hours after the onset of "toxic vomiting."

Altogether 1107 completed cases have been investigated by the writer during a period of 25 months from July 1919 to July 1921. In the early autumn of 1919 there was a marked rise in the incidence of diphtheria in the district served by the hospital, and during the next few months the disease assumed epidemic proportions, the number of admissions to hospital being the greatest for 20 years. The type of disease was severe, the case mortality for the latter half of 1919 being 10.2 %. The disease remained prevalent during 1920 with a case of mortality of 9.2 % and it was only in the summer/

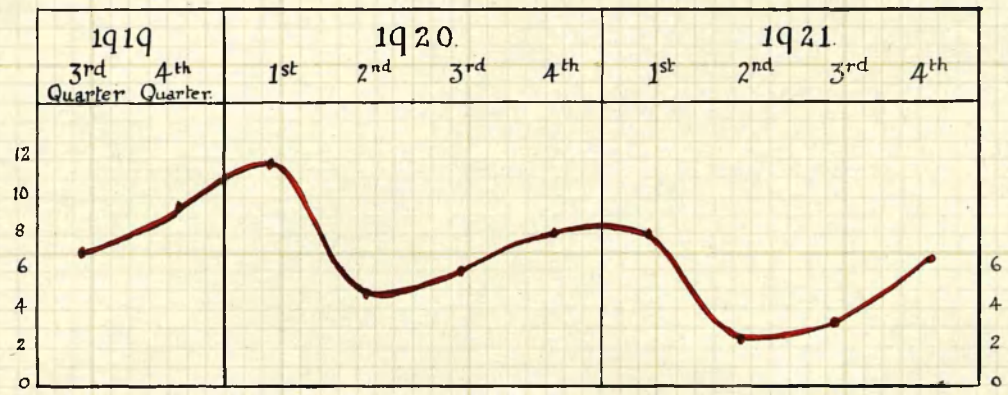
summer of 1921 that the admissions showed a tendency to reach the pre-epidemic level. The case mortality also showed a decided improvement being 7.3% for the six months ending June 1921.

The introduction of antitoxin has doubtless reduced the mortality from diphtheria. The figure given for cases treated in the hospitals of the Metropolitan Asylums Board for the years 1890-93, before the use of antitoxin, was 30.39% with a steady decline as antitoxin was more and more used. ( )

Diphtheria, however, still remains a dangerous and treacherous disease, which, as the figures in the following series show, may still be responsible for a considerable loss of young lives to the community.

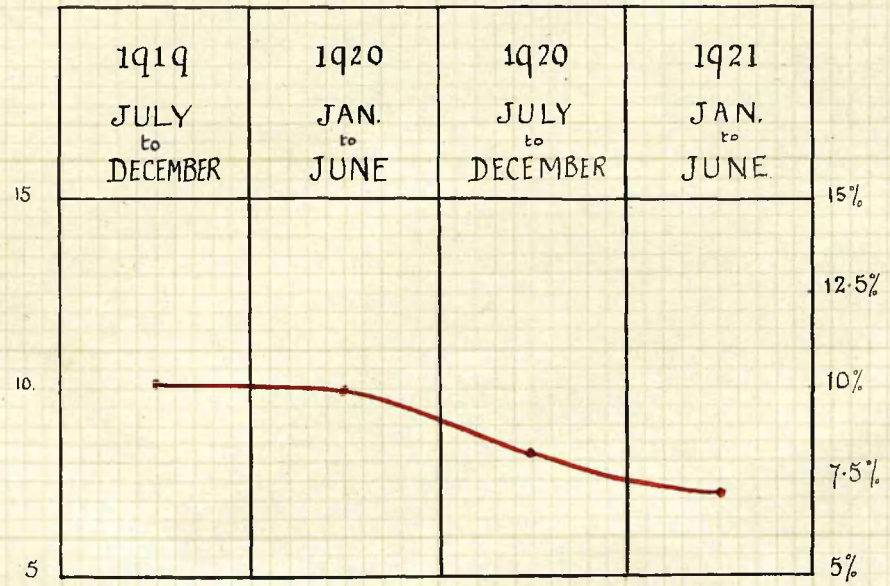
CURVE I.

Curve showing case mortality in each period of three months from July 1919 - December 1921 calculated on total admissions of cases notified as diphtheria.



CURVE II.

Curve showing case mortality in periods of six months from July 1919 - June 1921. "Patched throats" are here excluded, and periods of six months have been taken to obtain larger figures.



SECTION II.

Historical Outline.

Historical Outline.

Of the various infectious diseases which have prevailed from time to time Diphtheria is believed to be one of the oldest, the presence of a membraniform deposit on the fauces having been regarded from the earliest times as a morbid condition attended with considerable risk to life.

The disease appears to have been well known in Egypt, Syria and Palestime in ancient times. It is supposed that the Askara mentioned in the Talmud as a fatal epidemic was in fact Diphtheria, and although this work only appeared in the 5th century it transmitted old Jewish traditions. The word "askara" means literally "closure" and is allied to the word 'sakar' to close or to shut up.

Rashi, the learned commentator of the Talmud, remarks with reference to the Askara that sometimes "it breaks out in the mouth of a man and he dies of it". He further observes that sudden death ensues from suffocation. (4)

The first accurate description is that of Aretaeus (5) probably in the time of Augustus. The disease of which he has given a faithful picture in all its aspects, was even in/

in his time undoubtedly not new. He speaks of it as an affection which was known in Egypt and Syria and was so common that it received the name of Egyptian or Syriac ulcer. This observer describes the varieties of angina benign and malignant and notes the possibility of its extension to the respiratory tract.

Coelius Aurelianus at the end of the 3rd century, describes the barking sound of the voice and its occasional complete extinction. His reference to the passage of fluids into the nose in swallowing probably refers to the paralytic symptoms of the disease. (4)

In Western Countries according to Hirsch (6) the first mention of Diphtheria is in the 6th century. In the chronicle of St. Denis for the year 580, a "pest" is mentioned which went by the name of "esquinancie", corresponding to "squinantia" a name subsequently applied to Angina Maligna. Baronius writes under date 856 of a "pestilentia faucium" which occurred at Rome, and of a similar epidemic in 1004. Short (7) refers to a kind of angina which was prevalent in England in 1389 and carried off a large number of children.

The first trustworthy epidemiological information about Angina maligna dates from the end of the 16th century.

About the year 1581 a great pestilence marched over Spain/

Spain where the disease, known as "garrotillo", or morbus suffocans was epidemic year after year for fully thirty years. Again in Italy malignant sore throat was epidemic in 1610 but it was not until 1618-42 that it became general in that country. (6)

There are many descriptions of the disease given by contemporaneous writers and numerous clinical points are noted.

Villa Real (1611) observed the nature of the membranous deposit not only in the living subject but by post-mortem examination. Severino in 1643 clearly described diphtherial paralysis (4) and this is apparently the first direct reference to the paralytic sequelae of the disease. These were also noted in 1748 by Ghisi who observed an epidemic of the disease at Palermo. In 1749 Marteau de Grandvillers described an outbreak in Paris and the elder Chomel in detailing the symptoms accurately depicted diphtherial paralysis. (4)

From the middle of the 16th century to 1740 few descriptions appeared of malignant angina, but from that period onward there is a tendency for writers to designate the disease under two different denominations, croup and malignant angina, according to the predominance of some or other of its symptoms. (8)

Hirsch states that a great extension of the prevalence of/

of diphtheria took place in the early part of the 18th century, and it became epidemic in France about the middle of that century. From France it extended to Holland and eventually reached England, where it was described by Fothergill (1748) Starr (1752) and Huxham (1751-53). (4)

The next record from Britain is the important work of Francis Home on the nature, cause and cure of Croup. (9) He designated the condition, suffocatio stridula, from the stridulous voice, hoarseness and laborious breathing, and described two forms, the "benign or catarrhal", and the "membranous", the latter being attended with considerable risk to life.

Acting on the impetus given by Home's treatise the Société Royale de Médicine de Paris in 1785 offered a prize for an essay on Croup. Again in 1807 Napoleon I., whose nephew succumbed to an attack of this disease, offered a prize for a thesis on the same subject. This led to the publication of the valuable work of Albers and Jurine which were worthy predecessors of the classical memoirs of Bretonneau. (7)

The latter owed their origin to an alarming outbreak of diphtheria at Tours in 1818, and it was the observations made during this and subsequent epidemics which Bretonneau published/

published in his monumental treatise on Diphthérite or pellicular inflammation of the mouth, pharynx and air passages. (8) In his opinion, the production of membrane by the actual virus was the characteristic mark of the disease. In the severe apparently gangrenous forms he found at the autopsy not the expected gangrene of the mucous membrane but a "pellicle" of a greyish green colour lying upon the slightly altered tissues. This was the source of the pestilential odour which had suggested a gangrenous condition.

The observation that adults who were suffering from angina maligna could infect children with typical croup and the fact that the deposit on the tonsil and pharynx exhibited the same structure as the membrane in croup, convinced him that croup and malignant angina must be dependent on "the same disease-producing factor." (7)

In connection with the symptom complex described in the introduction it is interesting to note that Bretonneau, in his fifth memoir, mentions that several examples occurred of these sudden cases of toxaemia which destroy life, without closure of the glottis. Again, in his first memoir he notes one case, out of fifty-five post-mortem examinations, in which the membrane did not pass beyond the commencement of the oesophagus or entrance to the glottis.

"This/

"This child appeared to die of exhaustion on the 15th day of illness without any other symptoms than continual vomiting."

Bretonneau in his memoirs apparently only mentions two cases of paralysis. The first is that of M. Herpin who contracted severe diphtheria with membrane on both tonsils and uvula. He subsequently developed confusion of sight, constriction of the throat, paralysis of the palatine vault and regurgitation of fluids through the nostrils. Later there was tingling in the hands and feet and loss of all tactile power.

The second is that of George St.B. aged 12 years who passed through a severe attack of diphtheria. At the end of three months this boy "was able to walk by himself but looked at his feet to know if they touched the ground. They still remained so destitute of tactile power that he appeared to himself to be walking in the air." Bretonneau thus fully recognized that Paralysis was a possible complication or sequela of Diphtheria.

Jenner (10) in 1861 clearly described the symptoms in a series of clinical cases. In the chapter on Paralysis the snuffling voice and regurgitation of fluids through the nose and the derangement of vision are all mentioned. He also describes/

describes a case of head drop and refers to the ataxic gait which follows severe diphtheria.

We now come to the brilliant work of Klebs and Loeffler and the discovery of the true aetiological factor in the causation of Diphtheria.

In 1883 Klebs stated that in sections stained with methylene blue, he had found near the surface of the membrane rods of uniform length and extremely slender with frequently spores at each end.

Loeffler using solidified blood serum was able to obtain pure cultures of these rods, and in 1884 published a paper which showed that he had satisfied Koch's postulates with regard to diphtheria.

In 1890 Loeffler reviewed the investigations of other workers and communicated the fact that two guinea-pigs which survived inoculation with diphtheria bacilli suffered from extensive necrosis of the skin followed by paralytic phenomena. After surviving the paralysis, the animals were capable of withstanding repeated inoculations with cultures of the bacilli without considerable reaction.

He also succeeded in obtaining from both cultures a toxin which he postulated as the disease producing agent of the diphtheria bacillus. (7) The latter finding was confirmed by Roux and Yersin.

In/

In 1890, the same year in which Loeffler made the communication mentioned above, C. Frankel and Behring began to work on artificial immunization against diphtheria, and further experiments carried out by Behring and Wernicke soon led to the desired result. The latter workers were able to obtain from guinea pigs immunized against diphtheria a serum which when injected into other guinea-pigs protected them against more than a lethal dose of diphtheria cultures or toxin, and thus the question of immunization was substantially solved. (7)

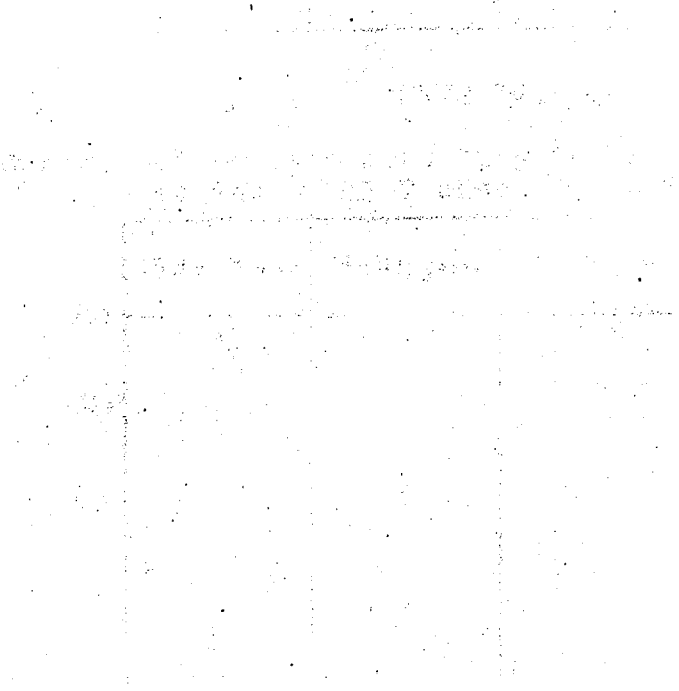
Larger animals were then used for inoculations and eventually a serum was obtained from the horse which would be used in the treatment of human beings.

We are now in a position to say that we know the real cause of Diphtheria, namely the Klebs-Loeffler bacillus. This organism produces an exotoxin which lends itself to investigation and on which an enormous amount of research has been done. We have also in antitoxin a specific antidote which has stood the test of time.

In spite of these considerations, however, we cannot say that the treatment of diphtheria is a simple matter or that a favourable termination is certain in many of the severe cases.

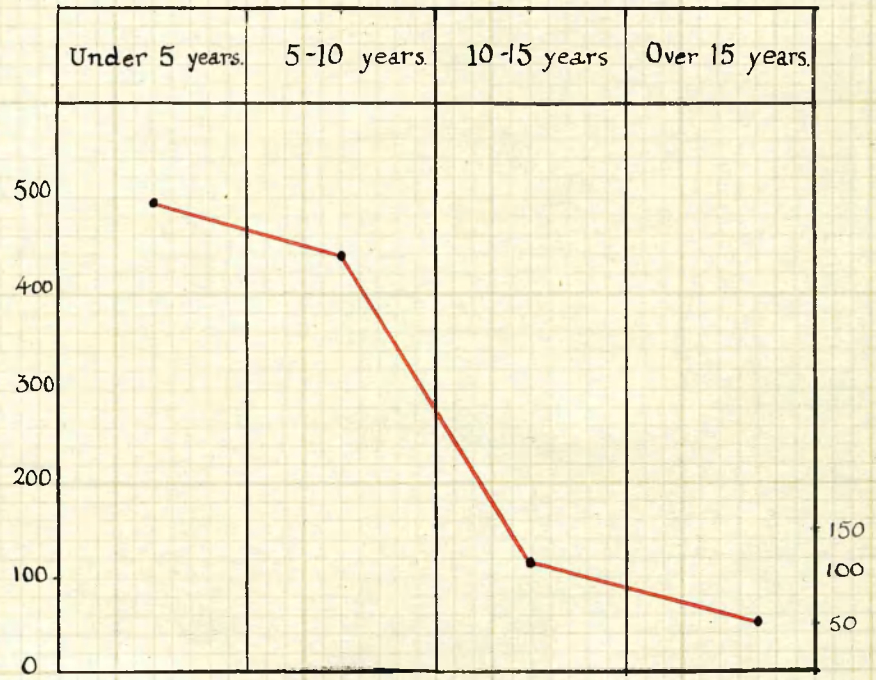
There are, in fact, many problems to be elucidated in the/

the pathogenesis of this morbid entity which has, from the earliest times, been looked on with dread by the communities affected. Further, a disease which may cause, in spite of modern methods of treatment and diagnosis, a mortality of nearly 15% in children under five, can scarcely be said to have lost all its terrors.



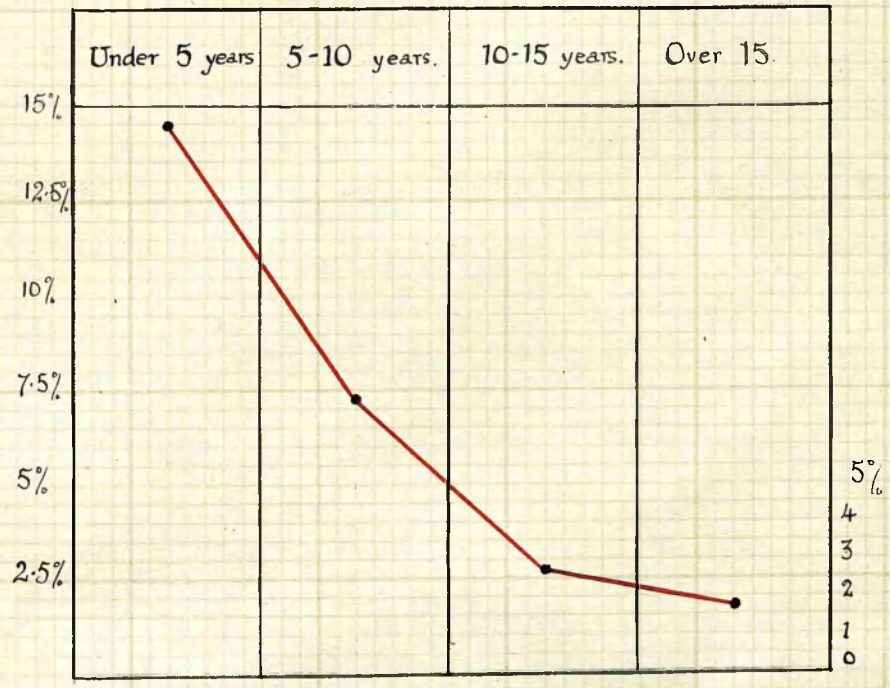
CURVE III.

Curve showing the incidence of diphtheria in relation to age in series of 1107 cases (July 1919 - July 1921).



CURVE IV.

Curve showing case mortality in relation to age in same series of 1107 cases. (See Table 1).



SECTION III.

Pathogenesis.

Pathogenesis.

In the human subject diphtheria most commonly presents itself as an affection of the mucous membranes of the throat and air passages. An exudate is formed and apparently toxic substances are absorbed into the circulatory and lymph streams.

These toxic substances are responsible for the symptoms and complications of the disease, e.g. muscular weakness, albuminuria, syncope and paralysis. In the air passages mechanical obstruction to respiration may be caused by the exudate.

All these conditions have been produced experimentally in animals by the injection of the bacilli or its toxins, and if the animal survive long enough paralytic phenomena may occur simulating post-diphtheritic paralysis in man. (11)

Thus we may safely assume that the bacilli in the local lesion produce a "poison" which is absorbed into the system.

The evidence of statistics since the introduction of antitoxic treatment goes to prove that this "poison" can be to a large extent neutralized by the administration of the specific anti-body even when the disease is fairly well established/

established. The figures in the present series, however, show that the disease in spite of active treatment still proves fatal in a certain percentage of cases and of those which recover many may develop paralysis in a severe form, and only do recover after a long period of slow convalescence.

Presumably the "poison" has been absorbed from the local lesion in the hours or days before antitoxin treatment has had time to take effect,and yet it is often two, three or even more weeks before any paralytic phenomena present themselves. Even in the early fatal cases, the local lesion is usually healed and the throat free from diphtheritic exudate before the grave symptoms appear. In the thesis an attempt is made to arrive at an explanation of this latent period, and the writer also considers the possibility of the early circulatory failure being due to a lesion of the nervous system in addition to myocardial degeneracy.

Many theories have been brought forward to explain the causation of this so-called "cardiac paralysis" and it has been ascribed by various writers to :-

(1) Vagus paralysis.

(2) Myocardial degeneration due to direct action of toxin.

(3) Paralysis of the vaso-motor centre.

(4) Degeneration of the suprarenal glands.

(5) Damage to the endothelium of the capillaries causing "lymph-logging" (Harding). (12)

observed that stimuli, acting directly or reflexly on the vaso-motor centre of healthy animals and thus causing a marked rise in blood pressure, produced little or no effect in animals suffering from diphtheria intoxication.

On the other hand they found that the heart was able to deal effectively with an increased supply of blood when this was supplied by abdominal massage.

Rolly (1899) holds that the early fall in blood pressure is due to vaso-motor paralysis and that the heart paralysis is not secondary to an insufficient supply of blood. He points out that when vaso-motor paralysis is complete and the blood pressure is low, if artificial respiration is maintained the heart goes on beating for hours.

He was unable to confirm Fennyvessey's (1896) observation that diphtheria toxin acts directly on the heart muscle, even when 60 lethal doses were introduced into the small volume of a heart-lung circulation. The toxin never produces an immediate effect but after a definite latent period a heart paralysis comes on, independent of the earlier vaso-motor paralysis. After this latent period is passed replacement of the toxic blood by normal blood can never save the life of the animal even when introduced before the onset of heart symptoms.

These/

These three observers are apparently agreed that there is in diphtheria-intoxicated animals a true vasomotor paralysis and that this is the cause of the great fall in blood pressure.

Rolly's experiments also seem to show that toxin does not act immediately or directly on the heart muscle, but that after a latent period the "initial" dose of "poison" can go on acting after the toxin in the blood stream is removed.

This would correspond to what happens in the human subject, when circulatory failure ensues in spite of antitoxin treatment, the "initial dose of poison" being apparently "fixed" and out of reach of the circulating specific anti-body.

The fact that diphtheria toxin can act on the central nervous system is clearly demonstrated by Dean's work on intracerebral injection of toxin in animals.

After giving the toxin by this route, he found that in many instances typical late paralysis occurred, beginning after an interval during which the animal seemed perfectly well. (13)

This is analogous to what is seen clinically in the human subject, where paralysis may develop late in the disease, even although antitoxin has been given.

Morbid Anatomy. I. Nervous System.

With regard to the nature of the nerve lesions in post-diphtheritic paralysis, S. Martin (14) has shown the degeneration to be of the nature of a true peripheral neuritis. In rabbits treated with albumoses and organic acids extracted from the tissues of patients dead from diphtheria, he found on post-mortem examination that the portion of the nerve fibre primarily affected was the white sheath of Schwann, which breaks up and finally disappears. The axis-cylinder may be unruptured when the white substance has disappeared, but it finally ruptures and the nerve below undergoes Wallerian degeneration. In an individual nerve many fibres remain unaffected. Sensory nerves may also be involved, but he was unable to detect any degeneration in the cells or nerve fibres of the pons and medulla.

He also investigated the condition of the nerves in two fatal cases of diphtheria in the human subject.

In one case where the disease proved fatal in five days, he found degeneration of the right phrenic nerve. In the other, which lived for four weeks, there were changes in the phrenic nerve and the nerves to the vasti muscles and palate. The nerves showed the same appearances as those produced in the experimental animals by the albumoses and organic acid.

He/

He also states that there may be widespread degeneration without palsy. In one rabbit which showed during life only slight signs of weakness every small nerve examined showed degeneration.

Dejerine in 1878 (15) described changes not only in the peripheral nerves, but in the cells of the anterior cornua.

Rainy from a series of experiments concluded that diphtheria paralysis was associated not only with changes in the peripheral nerves, but also with alterations in the cord itself.

Arnheim in 1891 found no changes in the medulla or nerve centres, but parenchymatous and interstitial degenerations in the peripheral nerves.

Woodhaven described changes in the trophic centres of the nerves after 24 hours of intoxication and believes that this accounts for the changes seen in the peripheral nerves as described by S. Martin and Dejerine.

Vincent, on the other hand, found lesions of the cardiac plexuses in a case of diphtheria dying with symptoms of cardiac paralysis. These were of the nature of a parenchymatous and atrophic neuritis. In this instance the pneumogastric centre and nerve were normal. (15)

Mallory (16) examined various parts of the nervous system/

system in 29 cases of diphtheria which were selected either on account of cardiac symptoms, paralysis, or the severity of the disease.

He describes in the pons and medulla slight to marked diffuse fatty degeneration of the white substance, and states that all the nerves examined, including the vagus, showed various degrees of fatty degeneration from slight to extreme. This seemed almost invariably to begin in the myelin sheath. In no axis-cylinder which could be positively demonstrated was there any evidence of fatty degeneration.

It is thus seen that, although observers differ as to the exact nature and extent of the nervous lesion in diphtheria, all are agreed that there is a definite degeneration of nerve elements.

II. Heart.

With regard to the microscopical appearances in the heart, numerous observations have been made.

Hayem,(1870) who was the first to make a careful and systematic study of the heart in Diphtheria,found granular and fatty degeneration, also acute interstitial myocarditis. (15)

Rosenbach (1877) found waxy degeneration and cellular infiltration/

infiltration.

Romberg (1891) noticed great differences in the extent of the lesions in sections from different parts of the heart. Degeneration of the muscle fibres with occasional vacuolation was the most common lesion.

Interstitial changes were found in all the eight cases examined. These occurred in foci and were most common beneath the pericardium.

Vincent found changes in the cardiac plexuses and refers to the work of Lantino who performed unilateral section of the vagus in 16 animals,and found lesions of the myocardium at the autopsies. Vincent felt justified in drawing the conclusion that the degenerative changes found in the heart muscle were secondary to those in the cardiac nerves. (15)

Eppinger (17) reporting on 18 cases of post-diphtheritic paralysis of the heart was of opinion that the paralysis was due to changes in the heart muscle excited by the diphtheria toxin and that there is a true toxic myolysis. The cases examined by him died 6 - 16 days after the onset of the disease.

Mallory (16) divides the lesions found in the heart into two groups:- (1) Fatty degeneration, (2) Interstitial myocarditis and,associated with the latter,mural thrombi.

(1) Fatty degeneration is sometimes the only recognis-

able/

able change in the muscle fibre, but it also accompanies the more advanced forms leading to necrosis. Fat occurs in the muscle fibres in over half the cases, and in those which die early in the disease it is generally the only lesion.

Interstitial myocarditis occurs in two forms: (a) Focal collections of cells of the lymphocyte series, often typical lymphoid and plasma cells being present. (b) Hyaline degeneration and necrosis of the muscle cells which are invaded by endothelial cells and polynuclear leucocytes.

Thrombosis within the cavities of the heart is a fairly common condition in cases of rather long duration and is due to a primary necrosis of the endothelium. The lesion is associated with the interstitial changes. (16)

In early fatal cases of diphtheria, the writer has found that there may be little abnormality in the heart to be seen with the naked eye at the autopsy.

In the case of E. L.....m, aged 7 years, who died from faucial diphtheria on the 8th day of illness, the heart was found to be normal in appearance. The muscle was firm and looked healthy. The valves were normal, and no mural thrombi were found in the cavities of the heart.

The liver was congested and showed no fatty degeneration. The spleen was enlarged soft and friable, the malpighian corpuscles being large and prominent.

The/

The writer has frequently found this type of autopsy in cases dying on the 7th or 8th day, one which, as far as the heart is concerned, gives findings which are largely negative.

Where death does not ensue till well on in the 3rd week (17th or 18th day), the heart may be dilated and the muscle pale and soft. There may be ante-mortem clots in the cavities. The liver and kidneys are generally in an advanced state of fatty degeneration.

Ante-mortem clots, as Mallory (16) has pointed out, are associated with interstitial myocarditis. The writer found these in seven cases of diphtheria, the clot being present in all cases in the auricles. In two a thrombus was found in the right ventricle in addition. In one case dying on the twelfth day of illness the ante-mortem clot was present in the left ventricle.

Woollacott (18) has described the presence of ante-mortem clot in the left ventricle in a case dying on the seventeenth day of illness.

Marfan quoted by Harding (12) deals with the subject of mural thrombi in detail.

It is thus seen that lesions of the myocardium do undoubtedly occur in diphtheria, and the fact that these should constitute a feature of ~~or in~~ the morbid anatomy is not/

not surprising in view of the clinical symptoms. Authorities, however, are not agreed as to the true explanation of the pathological findings.

Vincent held that the myocardial degeneration was secondary to changes in the nervous system, but most observers seem to consider that there is a true myolysis due to direct action of toxin. The experimental evidence quoted above is certainly against this latter view, and points to a lesion of nerve elements as a factor, at least, in producing cardiac failure, if, indeed, it is not the main cause of the circulatory disturbance which is such a marked feature of the disease.

Leaving this aspect of the subject the writer wishes next to consider the possible paths by which the toxin may reach the nervous system.

Until recently most authorities seem to have accepted the view that the toxin circulating in the blood stream acted on the nerve elements, in other words, that the toxi-infection was haematogenous.

Many of the pathological findings and symptoms can be explained by the action of a toxin in the blood,and where a massive dose has been absorbed in an advanced case, there is no doubt that this path comes largely into play. It does not, however, in the writer's opinion, entirely explain the sequence/

sequence of events in "cardio-vascular paralysis", or the nerve involvement which occurs late in the disease. With regard to the former it is conceivable that toxin may still be present in the blood when signs of circulatory failure show themselves. In the case of late paralysis, however, occurring many weeks after the throat is free from exudate, one would expect all the toxin in the blood stream to have combined with specific antibody.

Waldhe,(19) in an interesting paper on a series of cases of cutaneous diphtheria, has brought forward evidence to show that the path of infection may be an ascending one in the lymphatics of the nerves, and that the initial paralysis is related anatomically to the situation of the infective focus.

He quotes Guillain and Laroche as having called attention to this significant relationship between the primary lesion and the initial paralysis. On the other hand, observers have recorded the absence of palatal involvement in certain cases of extra-faucial diphtheria.

Leiditz (20) describes a case of diphtheria of the vagina and natal cleft where the first nerve involvement showed as a paralysis of the bladder. This, however, was followed by paralysis of the palate and derangement of vision.

With regard to the possibility of a lymphogenous path of infection/

infection, the work of Orr and Rows (81) on the subject is extremely important.

They quote the writings of Marie, Morax, Guillain, Sicard, Bauer and others whose experiments give ample evidence of the fact that organisms and toxins can reach the central nervous system along the lymph-paths of the peripheral nerves.

They themselves carried out experiments on rabbits and dogs. Celloidin capsules containing organisms (S. Aureus) were placed in close proximity to the sciatic nerve or under the skin of the cheek. Their experiments were divided into two groups according as the capsule remained intact or not. The evidence from these experiments left no room for doubt that the lymph stream in nerves is an ascending one and that organisms and toxins can be carried to the cord by that path.

Fatal cases of various infections examined post-mortem confirmed the results of their experiments. Not only was this path of infection clearly demonstrated, but there was also a perfect similarity in the type of reaction, and this varied with the degree of intensity of the irritant.

Walshe in his paper draws attention to the fact that analysis of his series of cases showed three elements in the symptom-complex:-

(a) a local paresis related anatomically to the infective focus;

(b)/

(b) a paralysis of accommodation like that seen in faucial diphtheria;

(c) a polyneuritis.

He further traces the resemblance between the symptom-complex and the modern conception of Tetanus which we owe to Meyer and Ransom. (22) From experiments on animals these workers found that when tetanus toxin was injected subcutaneously, it passed into the lymph spaces and vessels and could be recognised in a few minutes in the thoracic duct, but no toxin was found in the cerebro-spinal fluid.

If the animal was first protected by a large dose of antitoxin and a small dose of toxin was given into a motor nerve, a local tetanus resulted. If a sensory nerve was injected, neither local nor general tetanus ensued, while injection into a posterior root caused hyperaesthesia (Tetanus dolorosus).

From these and other facts they concluded that the transport of toxin takes place along the motor nerves and that the transporting medium is not the lymph stream but the protoplasm of the neurone, for otherwise the occurrence of Tetanus dolorosus is inexplicable.

They divided the symptom-complex in man into three stages, local, specific and general.

Walshe puts forward the hypothesis that in faucial diphtheria/

diphtheria with paralysis, the palatal involvement is due to local infection along the nerve, corresponding to local tetanus. The ocular paralysis he looks on as the result of the selective affinity of diphtheria toxin for certain elements of the nervous system, while the polyneuritis would correspond to generalised tetanus.

Another example of selective action of diphtheria toxin is the effect on the suprarenals which has been observed in diphtheria injected guinea-pigs. **Abramon** (23) has studied this lesion particularly and believes that it consists in degeneration and final disappearance of the chromaffin substance and of the medullary cells. He is of opinion that this together with degeneration of heart muscle is of great importance in causing the characteristic vascular failure.

In connection with this action of diphtheria toxin it is interesting to note the development of the medullary part of the suprarenal, which according to Geikie Cobb (24) is originally really part of the sympathetic system.

That some portion of the "poison" produced by the diphtheria bacillus has an affinity for nerve tissue is evident in view of the symptoms and pathological findings, and it seems reasonable to suppose that like other "poisons" it may have a specific or selective action on certain elements in the nervous system.

Encephalitis/

Encephalitis lethargica is another disease in which the possibility of a nerve path for the infection has been entertained. Marinesco (25) states that in Encephalitis lethargica the virus is probably taken in by the mouth and nose or even by the glands, and passes up along the nerves.

M. Button (26) refers to this in his paper and endeavours to find an anatomical explanation for the symptom-complex which occurs, the facial paralysis, ptosis, abducent or other ocular paralysis. He states that the facial nerve supply(ing) the buccinator and labial muscles and probably the levator palati and musculus uvulae (lesser palatine branch of the spheno-palatine ganglion, via vidian and great superficial petrosal) could afford a mode of entrance. In the substance of the pons the ascending portion is in the closest relationship with the medial longitudinal bundle, and in all probability contributes fibres to that bundle. In addition it embraces the nucleus of the sixth nerve. The nucleus most intimately related to the medial longitudinal bundle is the oculo-motor. The trochlear and abducent nuclei are also, of course, closely placed to the same bundle.

This anatomical nerve path, however, would apply equally in diphtheria, especially where the uvula and soft palate are involved in the local lesion.

In connection with diphtheria also M. Button points out that the causative organism is living and pouring out its toxin on/

on the walls of the pharynx, separated by a devitalised mucosa from muscles innervated by the cerebral part of the accessory (by way of branches of the vagus to the pharyngeal plexus).

Toxins ascending along the fibrillae of these nerves would be conducted to the nucleus ambiguus which also contributes to the vagus motor fibres to the heart. This would explain the association of dysphagia and regurgutation of food with cardiac disturbance in post-diphtherial paralysis.

He states that he has seen an interesting example of the association of these nerve paths in a case of paroxysmal tachycardia. The patient in the early stages was sometimes able to cut short the attack by the act of swallowing, a reflex action in which the nucleus ambiguus would be pre-eminently concerned.

In the introduction it was stated that paralytic phenomena might be absent after a severe attack and yet be present after a comparatively mild one.

In Table 6 it is seen that out of 10 "very severe" nasopharyngeal cases 4 died and 4 developed paralysis. The remaining two showed no sign of nerve involvement. Other examples of a similar nature could also be quoted in connection with less extensive lesions.

In order to account for the fact that paralysis does not occur/

occur in some severe cases, one might suppose an element of lessened susceptibility in certain patients to the diphtheria (nerve) "poison", but another explanation of this circumstance may be the effective barrier which uninjured mucous membrane presents to the passage of bacterial poisons.

Meyer, Ransom, Nanki, Carriére (23) have shown that neither diphtheria nor tetanus toxin will produce symptoms when introduced intestinally. Even cholera poison does not pass through the uninjured intestinal wall. Apparently the actual passage does not occur until the wall has been injured by the growth of living bacteria.

In the case of diphtheria also, localised injury to the mucous membrane at the site of infection may be necessary to prepare a portal of entry for the toxic products.

While it is usual to guage the severity of the disease from the extent of the local lesion, it is also necessary to consider the patient's general condition. Some patients with extensive membrane may show little constitutional disturbance, whilst others with moderate local lesions may be more or less "toxic".

Further, the situation of the local lesion must also be taken into account. As will be shown later, patients with extensive involvement of the naso-pharynx are more likely to develop nervous sequelae than purely nasal or laryngeal cases. The/

The presence of membrane on the soft palate and round the uvula apparently gives rise to more absorption of toxin than a large area on the hard palate.

There is little doubt, however, that local tissue damage must also be taken into account to explain these facts.

In the writer's experience, severe paralysis has frequently followed in cases where there has been a "mixed" infection in the throat.

e.g. The girl J. B., aged 14, who had serious nerve involvement and was in hospital for over four months, had on admission oedema of the uvula and a brawny swelling on one side of the throat simulating a peritonsillar abscess. The following day uvula and soft palate were covered with membrane.

It is unusual for suppuration to occur in the adenitis accompanying diphtheria even when it is marked ("bull neck"), but in the only two cases in the present series where there was abscess formation in the submaxillary glands severe paralysis followed.

One case S. R. G., aged 2½, had membrane on both tonsils and right pillar, and was admitted on the 5th day of illness. The other E. S., 5½, who developed nasal voice, regurgitation, strabismus and partial diaphragmatic paralysis was admitted on the 2nd day of illness and had membrane covering/

covering two tonsils only.

In the local lesion in diphtheria it is unusual to find deep ulceration or much loss of tissue. The thin pellicle of diphtheritic exudate is found to be lying, as Bretonneau pointed out, "on the surface of slightly altered tissue." Nevertheless, it is reasonable to suppose that there is a varying degree of necrosis present. The actual tissue damage may be more marked in some cases than others, and thus a larger portal of entry is gained for the toxin past the natural barrier of healthy mucous membrane.

Now Meyer and Ransom state that it is possible for diphtheria toxin to be absorbed through the nerve endings, (37) and if these are damaged, presumably it would be more easy for the toxin to effect an entrance as is the case in Tetanus.

In precocious palatal paralysis, to be described later, it is believed that the lesion is one of muscle, a myositis due to direct action of toxin. (37)

If, however, muscle tissue can be damaged, it is not difficult to imagine that other tissues lying between it and the diphtheritic exudate can also be damaged, e.g., blood vessels and nerves, the latter especially, in view of the specific affinity of the "poison" for nerve tissue. The nerve endings may thus be lying exposed and bathed by lymph containing/

containing toxin which is constantly being poured out by the bacilli living in the exudate.

With regard to the circulatory failure in diphtheria, it is thus seen that the experimental evidence is in favour of a nervous lesion as the exciting cause rather than heart damage due to direct action of toxin. Further, in the human subject, while fatty degeneration and interstitial changes have been found in the heart by many workers, lesions have also been described in the central nervous system and its peripheral extensions. Opinion, however, is still divided as to whether the former are due to direct action of the diphtheria "poison", or are secondary to and caused by a primary nerve lesion.

With regard to paths of infection, no doubt in the early stages of the disease toxic products are circulating in the blood stream, but these ought to be rapidly neutralised by the antitoxin injected or derived from the body cells. It is difficult to see how these circulating toxic products can be responsible for symptoms which occur many weeks after the local lesion is healed.

That the path of infection to the nervous system may be a lymphogenous one has been more or less accepted in other diseases, and it seems that the possibility of its existence in diphtheria should at least be recognised, if it is not at present/

present wholly accepted.

Finally, the toxin may possibly be taken up by the nerve endings, absorbed directly into the nervous system and thus become "fixed" out of reach of specific antibody.

Further, if the analogy of tetanus could be continued and diphtheria toxin can travel along the protoplasm of the neurone, an explanation would be afforded of the latent period in the disease as it affects the human subject, where death may occur many days after the local lesion is healed, and severe nervous sequelae may develop five or six weeks after the onset of the disease.

SECTION IV.

Clinical Features.

Clinical Features.

Turning now to the clinical aspect of the question, the writer will endeavour to show how these theories as to the mode of action of the diphtheria toxin can be reconciled with the symptoms presented by patients suffering from the disease.

The cases in the series to be discussed were admitted to Plaistow Hospital over a period of seventeen months when the writer was in charge of five diphtheria wards (about 65 beds).

All the hospital records and case papers have kindly been placed at his disposal by the Medical Superintendent and thus facts have been obtained with regard to cases not in the writer's wards. The details, however, in the present section relate to patients who were under his personal care and observed by him throughout the whole of their stay in hospital.

For the purposes of this thesis a total of 1285 cases were investigated.

178 of these have been classified as having "patched" throats. This term is used to include all forms of septic throats not caused by the diphtheria bacillus, such as Vincent's angina, Follicular tonsillitis, Peritonsillar abscess/

TABLE 1.

Table showing relation of age to Paralysis cases and deaths in series of 1107 cases.

Age in Years.	Number of Cases.	Paralysis Cases. Recoveries.	Fatal.	Total.	Percentage of Paralysis Cases.	Total Deaths.	Case Mortality.
0-5	495	47	38	85	17.1	72	14.5
5-10	443	62	21	83	18.7	31	7.4
10-15	114	7	1	8	7.0	3	2.6
over 15.	55	4	-	4	7.2	1	1.8
	1107	120	60	180	16.2	107	9.6

TABLE 2.

Table showing relation of age to Paralysis Cases and deaths in 178 completed cases which were discharged or died during three months at the height of the epidemic. The corrected figure for admissions, excluding "patched" throats, for the same 3 months (Dec. 1919 - Feb. 1920) was 227, giving a case mortality of 10.1% which closely corresponds with figure in Chart II. (Section I.)

Age in Years.	Number of Cases.	Paralysis Cases. Recoveries.	Fatal.	Total Deaths.
0-5	94	5	10	18
5-10	63	13	3	5
10-15	17	3	-	-
over 15.	4	1	-	-

abscess, etc. As none of these cases showed any paralytic phenomena and none proved fatal, they are excluded from the series.

The remaining 1107 cases were all definitely suffering from diphtheria or gave positive cultures for Klebs-Loeffler bacilli. As is shown in Table 1, 180 developed some form of nerve involvement. This number includes 51 cases which proved fatal during the first three weeks and which have been classed as due to "Cardio-vascular paralysis." (Tables 10 and 11).

1. Age in Relation to Paralysis.

From Table 1. it is seen that the incidence of paralysis was greatest during the first ten years of life. In this age period the type was also found to be most severe. Twenty-five of the recovery cases passed through a severe attack presenting involvement of pharyngeal muscles, head drop or respiratory paralysis. Of these 17 were under 6 years of age, and 8 between the ages of six and ten.

Only four patients over the age of 15 years had nervous sequelae. Two of these had palatal paralysis and two cycloplegia in addition.

These figures are at variance with Osler's statement (28) in 1905 that paralysis is proportionately less frequent in children than adults. Ker (27) holds that broadly speaking the younger the patient the more liability is there for paralysis to develop, and Rolleston's figures also go to show the/

TABLE 3.

Paralysis (recovery) cases and total deaths in series of 1107 cases. Analysed with regard to day of illness on which antitoxin was first given.

Day of illness: Antitoxin first given.	Paralysis Recoveries.	Fatal. Syndrome and Late Paralysis	Fatal. Haemorrhagic.	Other Cases.
1st.	2	0	-	-
2nd.	16	4	-	5
3rd.	39	13	6	6
4th.	26	17	1	10
5th.	18	15	-	2
6th.	12	7	1	3
7th and over.	7	4	4	9
	120	60	12	35

TABLE 4.

Paralysis Recovery Cases and total deaths in series of 178 Cases at height of epidemic. Analysed with regard to day of illness on which antitoxin was first given.

Day of illness.	No. of Cases treated	Paralysis.	Total Deaths.
1st.	6	-	-
2nd.	38	2	1
3rd.	37	6	6
4th.	40	5	10
5th.	32	3	4
6th.	14	4	1
7th & over.	11	1	1

the rarity of serious paralysis accompanying diphtheria in adult life.

The youngest case of paralysis observed by the writer was in a twin aged four months who recovered and, when seen twelve months later, showed no ill effects from her severe attack of diphtheria.

2. Relation of paralysis to the time of giving serum.

In this connection, the value of the following observations must be qualified by the fact that in an insidious disease like diphtheria it is often extremely difficult to determine with accuracy the exact date of onset.

Of cases treated on the first day of illness (Table 3) none died and only two developed paralysis. In one of these the paralysis was mild, and as the other patient had a croupy cough and membrane on both tonsils, it is doubtful if the history in this instance was correct.

158 out of a total of 180 paralysis cases had serum injected for the first time after the second day of illness, and of the 107 fatal cases 98 were untreated before the third day of illness. The importance of early injection of serum is thus seen.

On the other hand it is interesting to note in Table 4 that 25 patients were treated after the fifth day of disease, with a case mortality of 8%. Rolleston (1) treated 396 cases/

Recovery Cases. TABLE 5.

Analysis of 120 Paralysis (Recovery) Cases to show incidence in relation to site of lesion:

Site of lesion.	No. of Cases.
No membrane. Paralysis on admission.	2
Nasal discharge only:	-
1 Tonsil	4
1 Tonsil + Nasal discharge	1
2 Tonsils	26
2 Tonsils + Uvula	18
2 Tonsils + Nasal discharge	13
2 Tonsils + Pillars or Palate	35
2 Tonsils + Pillars or Palate + Nasal discharge	13
Laryngeal (croupy cough, recession) + Membrane on 2 Tonsils.	1
Tracheotomy Cases. Membrane on one or two Tonsils 3 with nasal discharge 1 with lesion on uvula in addition.	7
	120

cases after the 5th day with a mortality of 9.09% and states that there is thus an obvious advantage even in the late injection of serum.

3. Paralysis in relation to the extent and situation of the local lesion.

(1) Faucial diphtheria.

In Table 5. 120 recovery cases of paralysis have been analysed to show the extent of the local lesion. This has a definite relation to the occurrence and severity of the subsequent paralysis. Attention has already been called to the fact that only a percentage of cases with a certain type of lesion develop nervous sequelae. This is well seen in Table 6. e.g. 10 cases had membrane on two tonsils plus pillars or palate and of these only seven showed signs of nerve involvement.

Extension of the membranous exudate to the uvula, pillars and soft palate, or the presence of nasal discharge in addition to faucial lesion increases the likelihood of paralysis occurring and being severe.

In Table 5. the two cases described as having no membrane had not been treated with antitoxin and developed paralysis before admission to hospital.

Two of the 4 cases which had membrane on one tonsil only were admitted on the 3rd day, one on the 4th and one on the/

TABLE 6.

Paralysis (recovery) cases and total deaths in series of 178 completed cases which have been analysed with regard to site and extent of local lesion.

Situation of lesion.	Total Cases.	Paralysis (recoveries)	Deaths Total.
No membrane on fauces	2	-	-
Nasal involvement only.	3	-	-
Membrane on 1 Tonsil	17	-	1 *
Membrane on 1 Tonsil + nasal discharge	4	1	-
2 Tonsils	63	7	4
2 Tonsils and uvula	17	2	3
2 Tonsils + nasal discharge	20	2	5
2 Tonsils + Pillars or Palate	10	5	2
2 Tonsils + Pillars or Palate + nasal discharge	10	4	4
Laryngeal Cases. 3 without Faucial lesion	14	-	-
Tracheotomy Cases. 7 without Faucial lesion	18	-	3 (secondary Broncho-pneumonia.)

* Patient age 2½ admitted 8th day of illness: "fading membrane one tonsil only." Died after being in hospital 8 hours.

the 6th day of illness. Each had a mild attack of paralysis, three having slight palatal involvement (nasal voice) and one strabismus only.

In Table 5. if the eight laryngeal cases and the two with no membrane are omitted, there remain 110 cases of paralysis. Of these no fewer than 105 had membranous exudate on both tonsils or more extensive affection of the fauces or nasal passages.

The analysis in Table 6. clearly brings out the same points with regard to paralysis and also shows that there is a definite relationship between the severity of the local lesion and the likelihood of a fatal issue supervening.

(2) Nasal diphtheria.

The naso-pharynx is commonly involved in severe faucial diphtheria and is denoted by the presence of profuse nasal discharge. This was present in 35 of the paralysis cases. On the other hand, nasal diphtheria without faucial lesion does not have the same serious import. In the present series there were 9 cases where only the nasal passages were affected. Among these there were no fatal cases and none developed paralysis. Rolleston (1) mentions only one case of paralysis in 30 cases of nasal diphtheria.

(3). Laryngeal diphtheria.

When diphtheria affects the respiratory tract only, paralysis is a rare sequela. Circulatory depression and toxaemia are also uncommon in purely laryngeal cases. During the eighteen months January 1920 - June 1921 there were 42 recoveries after tracheotomy. Of these, the 5 cases which subsequently developed paralysis all had definite faucial lesions in addition to the laryngeal condition. In Table 5. the seven tracheotomy cases all had more or less extensive lesions of the fauces. There seems to be much more absorption of toxin from the soft tissues of the fauces than from the mucous membrane of the trachea or larynx, even when these are involved to such an extent as to call for surgical interference. This circumstance is doubtless explained to a large extent by the microscopic structure of the mucous membrane in the respiratory tract.

Enlargement of the submaxillary glands is practically always present in severe diphtheria. In 85 of the paralysis (recovery) cases the adenitis was moderate or slight, and in 32 marked enlargement was noted. Only in two cases did suppuration occur. One case was noted as having no submaxillary adenitis.

Albuminuria is almost a constant feature in diphtheria and it was present in all the cases of paralysis except one. Albumen/

Albumen appearing early and persisting may be taken as giving some indication of the amount of toxaemia.

Length of stay in hospital.

Of the 25 severe paralysis cases, three were discharged at the end of three months. The others were in hospital for varying periods up to five months or more, the longest being 160 and 163 days. It will thus be seen that paralysis short of proving fatal adds enormously to the length of convalescence.

TYPES OF PARALYSIS.

A. Recovery Cases.

With regard to the various sites of nerve involvement, paralysis of the palate was, in the series, by far the most common, being noted in 105 of the recovery cases. (Table 7.) In 60 it was the only form. Its presence is revealed by the nasal character of the voice which becomes more marked when the patient says such test words as "Billy Buttons," "Strawberry jam," or "boiled beef and carrots." Where the paralysis is very slight, it may only be noticed when he sings or calls out to the other children in the ward. There may be difficulty in detecting the nasal character of the voice in small children, who may scarcely speak at all for weeks at a time and then only/

TABLE 7.

Analysis to show date of onset and frequency of each form of Paralysis in the 120 Paralysis (Recovery) Cases.

Week of Disease	Palatal	Ciliary	Oculo-Motor	Facial	Pharyngeal	Head Drop	Paralysis of Diaphragm	General Paralysis
1st	1	-	-	-	-	-		
2nd	20	-	-	-	1	-		
3rd	23	1	2	1	2	2		
4th	7	2	3	-	2	2		
5th	14	-	4	-	2	6		
6th	24	3	4	1	5	6	-	-
7th	15	1	12	-	8	7	5	1
8th	1	-	3	-	4	1	1	-
	105	7	28	2	24	24	6	1

only in a quiet voice which throws no strain on the partially paralysed part. One girl (M.K. aged 7 years) who had been teased at home about her accent or way of speaking, never spoke during the whole of her stay in hospital. There is little doubt that she had palatal paralysis as she passed through a severe attack and subsequently developed head drop.

In the more severe forms, regurgitation may occur, fluids being returned through the nostrils during the act of swallowing.

Palatal paralysis as a rule makes its appearance after the second week of illness and may then remain present for several weeks e.g. case 4. Table 9. where 28 days elapsed before the nasal character of the voice disappeared.

Palatal paralysis, however, may develop during the first fortnight of the disease, and the term "precocious" is then applied to it. This type was present in six of the fatal and 21 of the recovery cases (Table 7.) being always associated with a severe local lesion.

The only case where it was noted during the first week was in a child aged three years, who developed severe head drop and paralysis of the muscles of the back.

The others had attacks of more than average severity as may be inferred from the length of their stay in hospital.

Recovery/

Recovery Cases with precocious palatal paralysis:-

4 were in hospital 120 days and over.

6 " " 90 " " "

5 " " 80 " " "

6 " " 65 " " "

According to Ker (27) there is good reason for believing that in the "precocious" type the palatal weakness depends on local changes in the muscle i.e. a myositis caused by direct action of toxin. He states that it frequently occurs where there is severe local lesion and that this is also in favour of the above view, especially where unilateral paralysis follows unilateral lesions.

The writer has noticed that where palatal paralysis was present in the second week of illness, the nasal character of the voice frequently became much improved or almost disappeared during the third or fourth week, only to become more marked again when ciliary or severe forms of paralysis presented themselves.

While the most usual form of palatal paralysis is present only for a few weeks, the nasal character of the voice in cases with the "precocious" type may persist for a much longer period. In Cases 1 and 2 Table 9. it was still present on the 60th day of illness.

In/

In a boy, W.H. aged 15 years, it was present from the 10th to the 58th day and in a girl, B.R. aged 14 years, from the 9th to the 65th day. The latter patient passed through a very severe attack of diphtheria and had a systolic blood pressure of 64 mm. on the 16th and 18th day of illness. In this case the palate was paralysed one day before the membrane had disappeared from the throat. This patient later developed ciliary paralysis and was discharged well after being in hospital 100 days.

Ciliary paralysis was noted in only 7 cases but it must have occurred much more frequently than this figure indicates, as it is almost impossible to detect it in young children. Ker (37) in a series of 3422 cases gives 14 instances of cycloplegia occurring in 317 individuals with paralysis. Whereas Rolleston (1) in a series of 2,300 cases records 236 cases of ciliary paralysis occurring in 477 individuals with paralysis and states that it is the most common form of paralysis after that affecting the palate. Paralysis of accommodation seldom appears before the end of the 3rd week. In Case 2. Table 9. it was present from the 28th to the 57th day, and in case 3. from the 30th to the 65th day. In the patient B.R. aged 14 mentioned above the cycloplegia did not appear till the 32nd day and had passed off by the 65th day of illness.

Paralysis/

Paralysis of oculo-motor muscles. This is much more readily detected even in small children and occurred in 28 cases. The sixth nerve is nearly always involved giving rise to an internal strabismus.

Facial paralysis occurred in 2 cases only.

The right side was affected in a girl aged 7 who also had regurgitation and pharyngeal paralysis. In the other case a boy aged 4½, there was head drop: strabismus and paralysis of the left side of the face.

The Levator palpebrae Superioris was affected in only one case a boy D.C. aged 3 years who had head drop, and paralysis of the muscles of the back.

Paralysis of the pharyngeal muscles is always a sign of serious nerve involvement and is usually associated with paralysis of the palate or of the respiratory muscles. The main symptom is "food cough" i.e. a tendency to cough and splutter on attempting to swallow food. As fluids or solids may enter the larynx, this type of paralysis is in itself a serious danger to the patient. In the more severe forms salivation is present, the patient being unable to swallow the saliva which trickles out of the mouth and is an added source of discomfort. In the present series, 19 out of the 24 cases of Pharyngeal Paralysis noted, occurred in the fifth week/

week or later. One case only occurred in the second week of illness and in this instance it was associated with Precocious paralysis of the palate. It is unusual for pharyngeal paralysis to last much longer than a fortnight. In a case of general paralysis, to be described later, it was present for 15 days (41st to 56th day of illness).

Paralysis of respiratory muscles. This is the most serious form of nerve involvement excluding actual "cardio-vascular paralysis." It is, however, not necessarily fatal as paralysis of the diaphragm was present in 6 of the recovery cases. The symptoms of diaphragmatic paralysis include a reversed type of breathing and an "ineffective cough". The abdominal wall remains almost motionless or recedes during inspiration and the patient is able only with difficulty to expel the mucus which tends to collect in the air passages.

No case of intercostal paralysis was noted in the present series.

Muscles of the neck and trunk. When the former are affected a condition of head drop is produced. The patient is quite unable to raise the head and in some instances cannot even move it from side to side. Head drop was present in 24 cases and was always an indication that the patient had passed through a severe attack of diphtheria.

The/

The most marked instance of paralysis of the back muscles was in the boy D.C. aged 3 who had precocious palatal paralysis.

Paralysis of the lower extremities.

In small children the less complete forms may pass unnoticed and where the patient is kept in bed for a prolonged period the actual paralysis may have passed off before he is allowed to get up. Four cases, however, under 5 years of age had definite foot drop and two boys aged 12 and 18 years had well marked ataxia. The ataxic gait of the diphtheria convalescent is a feature of the disease and was present in every case where there was serious nerve involvement.

Loss of knee-jerks is also a fairly constant and early sign of severe paralysis, and while it is frequently the first to appear it persists longer than the other forms. It may be impossible to elicit the knee-jerks even when the patient is being discharged from hospital and has recovered from the more grave forms of paralysis.

In some of the more severe cases there may be loss of sensation in addition to the motor paralysis. The patient J.B. aged 14 had loss of sensation in both feet to above the ankles still present on the 92nd day of illness. Ten days later the gait was still typically ataxic, and even when she was discharged from hospital at the end of more than 4 months, the/

the patient had not quite recovered her normal mode of walking.

Paralysis of upper extremities.

This condition is much less common and was only present in the following case of general paralysis.

R.K. aged 3.8/12 years was admitted on the 3rd day of illness with profuse nasal discharge and membrane covering one tonsil.

A nasal twang in the voice was first detected on the 33rd day and two days later there was complete head drop. Food cough developed on the 41st day. The child's general condition then was poor and the pulse rapid. Nasal feeding was commenced and the foot of the cot raised on blocks. Two days later there was marked salivation indicating serious involvement of the pharyngeal muscles. It was thennoticed that the child had internal strabismus, foot and wrist drop. On the 47th day of illness there was diaphragmatic paralysis with ineffective cough.

During the next fortnight, the little patient lay in an apathetic state, quite helpless. The mental condition, however, remained clear. She used to cry out feebly to have an arm or a leg moved, since at this period she seemed to have no power even to bend her fingers and was quite incapable of turning her head from side to side.

After/

After ten days the respiratory paralysis was passing off and salivation ceased on the 56th day, but it was not until the 67th day that the breathing became really normal. On the 79th day she was able to eat solid food quite easily and 4 days later nasal feeding was discontinued.

She eventually made a good recovery after a long slow convalescence during which she literally learned to walk again. She was out of bed for the first time on the 137th day but it was not till the 163rd day of her illness that she was fit to be discharged to her home.

Fortunately the severe forms of paralysis pass off fairly quickly. In this case the acute paralysis of the diaphragm was present for less than a fortnight and the pharyngeal paralysis for fifteen days.

Paralysis of the sphincter ani is exceedingly rare and no instance of this condition occurred in the series. In the case just described there was incontinence of faeces for a few days when the patient was so critically ill, but this could easily be accounted for by her very weak condition and was probably not a true paralysis.

The following is a description of a very severe case of naso-pharyngeal diphtheria which presented many of the types of/

of paralysis already described. It also gives a very complete picture of the progressive nature of the paralytic phenomena and the risk to life which they involve.

F.B. aged 8 years (Case 1. Table 8) was admitted on 31st July 1919, in the fourth day of illness with extensive membrane filling the whole fauces. The membranous exudate extended over the soft and hard palate to the molar teeth and there was profuse nasal discharge. The submaxillary glands were markedly enlarged ("Bull-neck").

There was no laryngeal involvement but the amount of ~~involvemen~~ obstruction in the fauces and nasal passages made breathing difficult, and on this account tracheotomy was performed. Rectal feeds were given as it was impossible to pass the nasal catheter. On the eighth day the tracheotomy tube was removed and rectal feeds were supplemented by tube feeding through the mouth.

On the 11th day there was a nasal voice and on the 12th "food cough". Nasal feeding was then commenced and continued till the 25th day of illness. By the 34th day the patient was able to swallow and enjoy full diet, his general condition steadily improving. On the evening of the 42nd day he vomited twice and the following day the nasal character of the voice became more marked. There was persistent "food cough" and salivation, so that nasal feeding again became necessary.

On the 46th day there was complete head drop and two days later diaphragmatic paralysis supervened. The patient remained desperately ill for the next few days; the breathing was difficult and there was constant salivation. On the 53rd day the salivation had ceased, and there was slight general improvement. The pulse and colour were better and hopes of the boy's recovery were again entertained.

The following morning, however, these hopes were dashed to the ground, as he suddenly collapsed at 8.20 a.m., became cyanosed and almost pulseless.

Oxygen was administered continuously for 45 minutes and he gradually rallied, the pulse and colour improving.

This boy did ultimately recover. He was a wonderful patient throughout his illness, easy to nurse and had put up a great fight against heavy odds. That morning, however, he must have realised that he was very ill, as he said to sister while he was having oxygen, "I am not going to die, am I, sister?" This shows how acute the mental condition remains in diphtheria even when the patient is critically ill.

Rectal feeds were given that day but next day the salivation was less, and it was possible to give nasal feeds again. By the 64th day he was taking bread and butter and all fluids by mouth. On the 65th day ~~about this time~~ diliary paralysis was/

was noted for the first time but probably it was present for many days previously but had been missed when the patient was so ill. The pulse continued rapid until about the 100th day and a week later he was allowed to get out of bed for the first time. This boy was discharged well on the 19th December 1919 on the 145th day of his illness.

Reference has already been made (Sect.III) to Walshe's paper on cutaneous diphtheria and his suggestion that the ensuing paralysis could be divided into three stages, namely, "Local", "Specific" and "Generalized", analogous to the three stages in tetanus. The specific form in diphtheria, Ciliary paralysis, causes, however, a symptom which is not so easily recognised as the trismus of tetanus and is doubtless overlooked in many of the younger children. Nevertheless Rolleston (1) places it next in order of frequency to palatal paralysis. This seems to be in favour of Walshe's hypothesis that it is due to a selective action of the toxin and ought therefore, to be of frequent occurrence. Ker (27), however, states that palatal paralysis has occurred in more than one case in which there was no pharyngeal lesion and that, therefore, the palate is sometimes "selected".

The writer's experience has been that in these cases of severe paralysis where from the age of the patient it could be readily/

TABLE 8.

Analysis of six cases between the ages of 5 and 10 years to show a gradation in the severity of the attack.

Number of Case	Day of Disease Admitted.	Extent of Membrane	Submaxillary Adenitis.	Antitoxin Units.	Period during which Urine contained Albumen.	Remarks	Day of Disease Discharged
1. F.B. 8 yrs.	4th	2T + U + Hard palate + N (membrane present)	"Bull-neck"	50,000	4th-44th day.	Tracheotomy for Faucial obstruction.	145
2. E.G.B. 10 yrs.	3rd	2T + U + Soft palate R. + N	Marked Both Sides.	40,000	4th-30th 48th-51st	Profuse nasal discharge.	134
3. S.F. 7 yrs.	2nd	2T + U Soft palate, R. + N	Marked Both Sides	V. 24,000 34,000	3rd-36th	Profuse nasal discharge.	125
4. H.L. $8\frac{11}{12}$ yrs	3rd	2T + U Extensive thick membrane	Marked Rt. less left.	V. 32,000 24,000	6th-42nd	No nasal discharge.	94
5. J.P. $5\frac{8}{12}$ yrs.	4th	2T +one anterior pillar.	Slight	30,000	10th-11th days		75
6. R.E. $5\frac{1}{2}$ yrs.	3rd	2T	Moderate L. side only.	28,000	15th-33rd		55

T = Tonsils, U = Uvula, N = Nasal discharge. V = antitoxin given intravenously in addition to the routine intramuscular injection.

TABLE 9.

Analysis to show in the six cases detailed in Table 8 a gradation in the subsequent paralysis.

Number of Case	Local	Specific	"Generalized"			Remarks.	Out of Bed for 1st time	Discharged
	Palatal	Ciliary	Pharyngeal	Head Drop	Paralysis of Diaphragm			
(1)	11th to 60th	65th day	43rd	44th	46th	Rapid Pulse until 100th day.	109th	145th
(2)	11th to 60th	28th to 57th	49th	51st		Rapid Pulse 90th to 110th day.	116th	134
(3)	16th to 60th Loss of Sensation	30th to 65th					90th	125*
(4)	18th to 47th No loss of sensation**						77th	94
(5)	42nd to 59th						32nd ~~64th~~	75
(6)	31st for a few days						40th	55

The figures e.g. "11th to 60th" refer to days of illness:
Cases (3), (4), (5), (6) had no regurgitation.

**Case (4), H.L., No Ciliary Paralysis developed. 32nd day, knee-jerks present: no loss of sensation in palate.

*This patient was fit for discharge on 112th day but developed a mild attack of influenza.

readily demonstrated, ciliary paralysis has always been present. This was also found to be the case in patients not included in the present series.

Table 8. has been prepared to show in six cases between the ages of five and ten years a gradation in the severity of the attack, including the extent of local lesion, adenitis, albuminuria etc. Table 9. shows in these cases a corresponding gradation in the subsequent paralysis arranged in the three stages of Walshe's classification. In cases 1. and 2. there is a fairly complete picture of the paralytic phenomena in diphtheria. In Case 3. the nerve involvement stops short of the development of severe forms, while in the last three cases, it remains localized. In these also there is a decreasing severity in the nerve lesion.

The writer considers that a patient who has a nasal voice and cycloplegia e.g. Case 3. Table 9. must be looked on as being on the verge of passing into the third or generalized stage of paralysis. This type of case, which will generally have caused some anxiety during the first fortnight, should, therefore, be kept in bed and carefully observed for the development of serious symptoms even as late as the sixth or seventh week. A reference to Table 7. will show how frequently the severe forms of paralysis, which are a real danger to the patient/

patient, present themselves after the 35th day of illness. It is precisely for this reason that the patient in this type cannot be considered out of danger until the 49th day is passed. After that period it is most unusual for severe symptoms to present themselves for the first time.

On the other hand, should the stage of generalized paralysis be entered, the prognosis even then is good, since only eight in the present series of 1107 cases died of late paralysis, a very small percentage.

B. Fatal Cases.

From the analysis in Table 1. it is seen that while the incidence of diphtheria was mainly in children under ten years the case mortality was greatest in the first five years of life, 14.5%, and fell to nearly half that figure for the succeeding age period of five years.

The only fatal case over 15 years of age was that of a woman aged 33, who died from laryngeal diphtheria of the ascending type, (ascending croup) fortunately a very rare condition in adult life.

In Table 10. an analysis has been made of the total deaths in the series (107) to show the mode of fatal termination

TABLE 10.

Analysis of total deaths (107) in 1107 consecutive cases of Diphtheria to show mode of fatal termination.

Cases which died during first twenty-four hours	7
Tracheotomy	24
Haemorrhagic	12
Other causes	4
Hemiplegia	1
"Cardio-vascular paralysis"	51
Late Paralysis	8

TABLE 11.

Analysis of 59 Fatal Paralysis Cases to show week of disease at which death occurred.

Week of Disease	Number of Fatal Cases	Type
1st	11	"Cardio-vascular"
2nd	30	
3rd	10	
4th	-	
5th	-	
6th	2	Late Paralysis.
7th	5	
8th	1	

Seven of these were either moribund on admission or died within 24 hours of being admitted: too soon, therefore, for antitoxin to have had any effect.

Twelve were of the haemorrhagic type which is almost invariably fatal within a few days.

Twenty-four cases succumbed to secondary broncho-pneumonia following tracheotomy.

With regard to the four cases classed as due to other causes two died during the second week of illness and might have been included in the syndrome group presently to be described. They were omitted, however, as they did not give a complete picture of diphtheria toxaemia at that stage of the disease, persistent vomiting being absent.

One case (R.R. aged 7/12 years) was admitted with a positive nasal culture but it is doubtful if the cause of death should be attributed to diphtheria as the child was a congenital syphilitic who had passed through a severe attack of gastro-enteritis and was in an extremely emaciated condition when admitted to hospital.

One case (L.A. aged 6 years) died in the 8th week of illness with persistent vomiting after apparently complete recovery from a moderate attack of diphtheria. In this case there were no signs of paralysis either in the early part of the illness or during the few days which preceded the fatal termination.

The death attributed to Hemiplegia occurred in a girl aged 4½ years who was admitted on the 4th day of illness with extensive membrane on the fauces and profuse nasal discharge. During the 2nd week palatal paralysis developed, the pulse became rapid and irregular and the general condition was poor. She rallied to a certain extent, however, and lingered on in a feeble state, nasal feeding being necessary throughout the illness.

On the 31st day she vomited and on the following evening had a convulsion with clonic spasms of the right arm, leg and right side of the face. There was slow nystagmus and the patient became unconscious. The clonic spasms continued until one hour before death which occurred on the 33rd day of illness.

This mode of fatal termination is quite unusual in diphtheria and Woollacott (18) states that only two cases of Hemiplegia occurred in 4,000 consecutive cases admitted to the Eastern Hospitals.

Rolleston in 1905 (29) described one case in 4407 cases admitted to the Grove Hospital since 1899. He quotes Baginsky's statement that hemiplegia differs from all other palsies in being primarily due to a vascular lesion.

The remaining 59 cases (Table 10 .) have been classified as due to "cardio-vascular" and late paralysis.

If/

TABLE 12.

Analysis to show date of onset and frequency of each form of Paralysis in the 8 fatal cases of late Paralysis.

Week of Disease	Palatal	Ciliary	Pharyngeal	Head Drop	Paralysis of Diaphragm
1st	-				
2nd	1				
3rd	1			-	
4th	2			1	
5th	2		-	2	-
6th	2		3	-	2
7th	-		2	2	4
8th	-	-	-	-	-
	8	-	5	5	6

If reference is made to Table 11. it will be found that ⅘ 41 of these died during the first fortnight and 10 in the 3rd week of disease.

If we omit the very rare case of Hemiplegia there is a gap of two weeks without any fatal case occurring.

The remaining 8 cases who died after the 35th day all presented symptoms of serious nerve involvement. As will be seen in Table 12. all these had palatal paralysis. One case, (N.M. aged 6.8/12 years) died on the 36th day after persistent vomiting associated with serious cardio-vascular disturbance. No respiratory paralysis was noted and the symptoms thus corresponded more to the "syndrome" type.

One case, aged 3 years, had complete head drop and the remaining six diaphragmatic paralysis.

In these cases dying late in the disease and presenting symptoms of serious nerve involvement, it seems justifiable to attribute the fatal issue to a lesion of the nervous system, Whether affecting the respiratory mechanism or causing an actual cardiac paralysis.

We now come to the consideration of the mode of death in the 51 cases which ended fatally in the first three weeks of the disease. The symptoms in these, although they varied slightly in each case, were sufficiently constant to form a definite/

definite syndrome which has been referred to in the introduction as "cardio-vascular paralysis."

The most characteristic feature in this symptom complex was the progressive fall in blood pressure which preceded the ultimate failure of the circulatory mechanism. This is well seen in the case of A.J. aged 8 years (Chart I.) The lowest reading in a fatal case, which could be accurately determined was 54 mm. This was taken at the brachial 36 hours before death occurred. (Case 3. Table 13 (a).) In recovery cases also the blood pressure may reach a low level. (Table 13b) and the prognosis must be increasingly grave as the reading approaches or falls below 65 mm., although such a pressure is not incompatible with recovery.

All the blood pressures were taken by the digital method with a Barton Sphygmomanometer.

The pulse although it is of low tension may remain quite regular until a day or two before death. In some cases there is a tendency for it to be slow and even in recovery cases this is sometimes well seen. G.C. aged 6 years had a pulse of 44 at 10 p.m. on the 9th day of illness. An hour later when the rate was 60 per minute there was a systolic blood pressure of 82 mm.

In other cases there is a tendency for the pulse to be more/

TABLE 13.

In this table the lowest systolic blood pressure reading is given in (a) 3 Fatal, (b) 3 Recovery Cases.

(a) Fatal Cases.

Age, sex.	Day of Disease Admitted	Lowest Systolic Blood Pressure.	Day of Disease on which Death occurred.
(1) E.L. $5\frac{9}{12}$ yrs. F.	3rd	64 mm. on 14th day	17th
(2) N.H. $6\frac{4}{12}$ " F.	2nd	56 " " 6th "	8th
(3) R.D. 7 " M.	4th	54 " " 10th "	12th

(b) Recovery Cases.

Age, sex.	Day of Disease Admitted	Lowest systolic Blood Pressure.	Extent of Paralysis.	Discharged	No. of days in Hospital.
(1) W.H. $6\frac{8}{12}$ M.	3rd	68 mm. 11th day	Palatal and int: Strabismus	100th	97
(2) B.R. 14 F.	5th	64 mm. 16th "	Palatal and Ciliary	104th	99
(3) R.B. 7 M.	3rd	60 mm. 11th " (62 mm. 12th day)	Palatal and Ciliary	86th	83

Chart No. 1.

Name A. J. aged 8 years M.

Extent of local lesion 2 + 1.

Submax: Adenitis - marked L. side

Antitoxin (Intramus) 52,000

DATE	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6	7	8	9	10
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.

Pept. Milk Feeds. Nasal Feeds. Rectal Feeds.

Adrenalin MV 4 hrly. Camphor MV 4 hrly. Adrenalin MV + camphor MV 4 hrly - alternately.

Syphilis Blood-pressure in M.M.

107 106 105 100 104 90 103 80 102 70 101 60 100 99 98 97 96

Pulse irreg: no radial pulse. Died 4-5 p.m.

PULSE	100	112	120	104	112	120	110	104	116	98	102	100	98	108	100	100	104	86	114	?	
RESP.	20	20	22	20	26	20	22	20	24	20	18	20	20	20	20	20	18	20	24	18	
MOT.	⊕			⊕			⊕				⊗							⊕			
VOM.	20*						.....	.....													

URINE

Q 3

R Acid

S G 1,026

D

A

B

	XV	XVI+	IV+	XXV	XXII	XXV	XIII	XIX	XVIII	IX											
	V.F.T	V.F.T	V.F.T	V F T	F.T	F.T	F.T	F.T	F.T												

more rapid than normal, or again the rate may be variable, dropping perhaps from 100 to 70 in a few hours. If the heart is auscultated the sounds may be found practically unaltered except for a slight softening of the first sound at the apex.

As the fall in blood pressure becomes marked, the pulse becomes more and more enfeebled and in some cases may be at times barely perceptible at the wrist two or even three days before death. Even then the heart will be found to be acting strongly, although the first sound may be altered and approximate in character more to the second. There is frequently no dilatation to be made out. As death approaches tachycardia develops and there is marked irregularity of the heart's action.

This was well shown in the patient A.J. Chart I. This boy was admitted on the 2nd day of illness with membrane covering both tonsils and profuse nasal discharge. The uvula, however, was oedematous, there was a tendency to "bull-neck" on the left side, and he had a "toxic" look, the face being pale and pinched.

In this case the heart was still acting regularly and strongly on the 11th day, 29 hours before death, the first sound then being of fair quality. Three hours later (2 p.m.) the pulse was first noted as being irregular. This irregularity became more marked and at 2 a.m. on the 12th day the pulse/

pulse was imperceptible at the wrist and remained so till death occurred at 4 p.m.

At 9.30 a.m. on the 12th day the first sound at the apex had lost its tone and approximated in character to the second, while at the pulmonic area it could only be faintly heard. Owing to the arrhythmia and recurring periods of tachycardia it was impossible to count the rate of the heart's beat. The liver, which was first noted as being slightly enlarged on the 10th day rapidly increased in size until on the 12th day the lower border was three finger breadths below the costal margin. There was no dilatation of the heart to be made out on percussion.

The boy's mind remained clear to the end. There was only slight restlessness and no paroxysms of the severe pain which is such a distressing symptom in some cases. ~~The Temperature~~

The temperature which may be raised two or three degrees at the onset tends to fall in a few days and may remain subnormal throughout. In fact, a subnormal temperature is so constant as to form a characteristic feature of the disease. This is well shown in the case of S.H. aged 6⅔ years (Chart II) who had the persistent "toxic vomiting", presently to be described, and presented a very complete picture of "cardiovascular paralysis".

As/

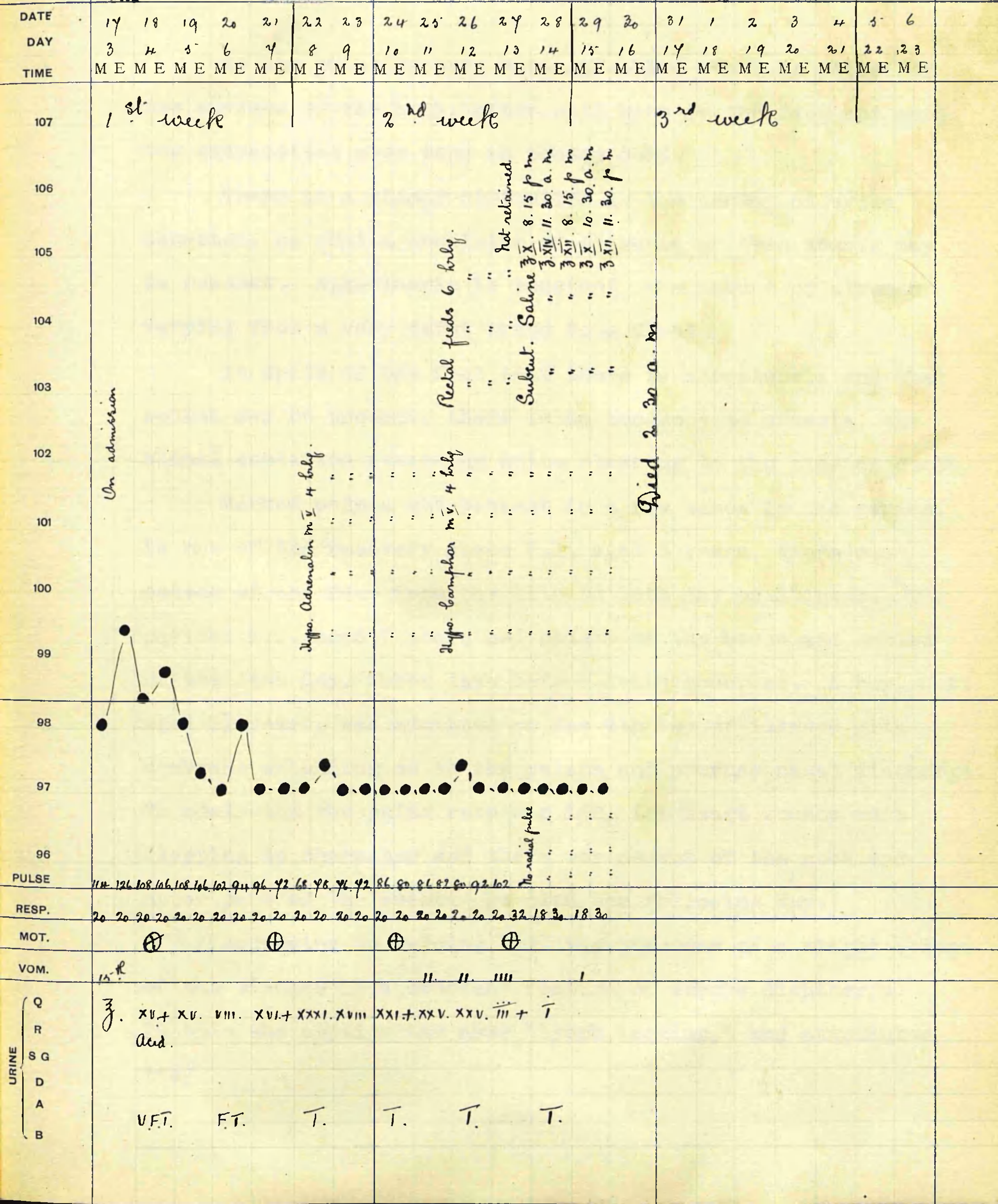
Chart No 2.

Name S. H. 6½ years. M.

EXTENT OF LOCAL LESION - MEMBRANE COVERING BOTH TONSILS.

SUBMAX: ADENITIS. - MODERATE BOTH SIDES.

ANTITOXIN. - 30,000 UNITS (INTRAMUSCULARLY.)



As the pulse becomes more enfeebled there is pallor of the surface of the body, often well seen in the face and ears. The extremities also tend to become cold.

There is a steady diminution in the amount of urine secreted, so that a condition of oliguria or even anuria may be reached. Albuminuria is constant, the amount of albumen varying from a very faint trace to a cloud.

In spite of the fact that there is albuminuria and that oedema may be present, there is no tendency to uraemia, the mental condition remaining quite clear up to the time of death.

Marked oedema was present in a few cases in the series. In one of the recovery cases V.H. aged 5 years, there was oedema of the face from the 11th to 18th day of illness. The patient F.C. aged 7 years had oedema of the hands and ankles on the 14th day, three days before death occurred. A boy, G.G. aged 3½ years, was admitted on the 4th day of illness with membrane extending on to the palate and profuse nasal discharge. On admission the pulse rate was 152, the heart sounds were flapping in character and there was oedema of the neck and upper part of the chest. He died the following day.

According to Harding (12) the presence of a slight oedema of the tissues is a constant feature of severe diphtheria. To this she applies the name "lymph logging," and attributes its/

its causation to a leakage of lymph through the capillary walls so that the blood becomes concentrated and a condition of oligaemia is produced. She came to the conclusion that the whole train of symptoms in the circulatory failure can be explained by this condition of "lymph-logging."

That damage to the capillary endothelium does occur, is well seen in haemorrhagic cases but these form only a small proportion of the total deaths. Further, a general oedema, in the writer's experience, has not always been present, and it is difficult to explain on this theory the symptom complex described as occurring in these early fatal cases.

In this type of fatal termination vomiting has always been a prominent symptom and it was present in all the fifty-one cases belonging to the syndrome group. In fact vomiting is to be looked on as a danger signal in diphtheria whether it occurs early or late in the disease. In Plaistow Hospital, it is the nurse's duty to report its occurrence immediately, as it may usher in a train of symptoms which have a very grave significance.

In some cases vomiting may be present and persist for two or three days before a fatal termination, in others death may occur twenty-four or even twelve hours after the onset of this symptom.

The/

The following two cases are examples of the rapid progress of circulatory failure which is sometimes associated with this so-called "toxic vomiting."

A.R. aged 2 years was admitted on the 5th day of illness with membrane on both tonsils and nasal discharge. He was progressing saitsfactorily when vomiting began at 12 noon on the 12th day of illness. The vomiting continued at intervals throughout the day, associated with all the signs already described as due to "cardio-vascular paralysis," and he died at 11.40 p.m. the same day.

J.P. aged 6 years was admitted on the 6th day of illness. The fading membrane only showed as a small patch onthe right tonsil. Although he was looked on as a serious case, there was nothing to mark his condition at the moment as specially grave. Vomiting began the following morning, the pulse became rapidly weaker throughout the day. At 5 p.m. the boy was in a state of collapse, with coldness of the extremities and no pulse perceptible at the wrist. He died at 7 p.m. the same evening.

In addition to the profound fall in blood pressure, there is great physical prostration and the patient may lie in an apathetic condition which to the friends and the uninitiated gives very little indication of the gravity of the situation. The state of weakness steadily increases, however, and the patient/

patient may literally be said to fade away in spite of all restorative and stimulating measures. In some the symptoms are extremely distressing. A condition of great restlessness supervenes, the patient tossing about incessantly. In a certain number, fortunately few, there may be agonizing pain often referred to the abdomen and this may be so severe as to make the patient scream out at times.

No unconsciousness comes to the relief of the sufferer, the restlessness and recurring attacks of pain continuing until at the end of twelve or perhaps twenty-four hours, a fatal termination brings release.

A consideration of this condition of early circulatory failure would be incomplete if reference were not made to the observations of Gunson whose work on the heart in diphtheria, according to Ker, entitles him to rank as an authority on the subject.

In his paper Gunson (30) divides the cases of circulatory inefficiency into two groups.

a. Those which maintain a normal rhythm.

b. Those which develop a marked arrhythmia with rapidity of the pulse.

The cases in Group (a) which usually die in the second week presented symptoms which correspond to the syndrome described in the thesis. In this class of case he has found that/

that the heart continues to act strongly until a few hours before death. The liver is only slightly enlarged or may remain normal in size. Bilatation of the heart is of late onset or absent.

The cases in Group (b) presented a syndrome which includes cardiac arrhythmia increase in cardiac and liver dulness and triple rhythm on auscultation. The onset of marked arrhythmia, he states is due usually to the presence of premature contractions, and is often associated with paroxysms of regular tachycardia. Such cases may rally repeatedly and make a complete recovery.

In fatal cases marked signs of circulatory failure may be wanting at the time of death which is due to failure of the respiration to which a diaphragmatic paralysis or bronchopneumonia may be contributory. This type of fatal termination corresponds to that which occurred in the paralysis cases dying late in the disease. (Table 12.)

Gunson holds that in Group (a) Vascular type there is a primary failure of the peripheral circulation with subsequent embarrassment of the heart's action. In Group (b) Cardiac type there is cardiac failure always preceded by the onset of severe arrhythmia.

"In both distubbed nervous control is held to be the essential factor."

Referring to the complex and widespread pathological findings he states that no conception of the circulatory failure will be complete which does not embrace the possibility of its dependence on pathological changes not only in the heart and its intrinsic nerve elements, but also in the blood vessels, the medulla ~~ib~~ oblongata, the vagi and the sympathetic system, as well as in the suprarenal glands.

Further it is impossible to assert on histological grounds that one structure is more at fault than another, and clinical observations are therefore the more important.

"These are strongly in favour of the view that the chief "factor in the circulatory inefficiency in diphtheria is "disordered action of the controlling nerve elements and not "myocardial degeneracy,thus bringing 'cardiac paralysis' into "line with the paralysis of skeletal muscles."

The facts observed by the writer in cases of "cardio-vascular paralysis" both during and since the epidemic bear out Gunson's statement on the early circulatory failure in diphtheria. Certainly the clinical picture points to a failure of the peripheral circulation at a period of the disease when the heart is still regular and acting strongly.

While the experimental evidence seems rather to favour a lesion of the nervous system as the cause of the fall in blood/

blood pressure, the pathological findings, as Gunson points out, are too widespread to prove that one structure is more at fault than another.

From careful consideration of the clinical features the writer suggests that the early circulatory failure in uncomplicated faucial diphtheria can, to a large extent, be accounted for by a loss of vasomotor control due to a lesion of nerve elements, probably in the central nervous system - due regard being given to the possibility of other factors being present such as myocardial degeneration and suprarenal insufficiency. Further, in some instances, the peripheral nerves may be at fault and the final cardiac failure result from implication of the vagus or the cardiac plexuses.

The cases which presented the symptom complex defined in the introduction and described in detail in this Section have, therefore, been included in the thesis and the term "cardiovascular paralysis" has been used to indicate that there is a profound disturbance of the vasomotor system as a whole.

SECTION V.

Prognosis and Treatment.

Prognosis.

In diphtheria with its accompanying nervous sequelae, the prognosis may be said to depend mainly on three factors, the date of giving serum, the extent and situation of the local lesion and the age of the patient. These have already been discussed in the preceding section in connection with the incidence of paralysis.

In general it may be stated that the earlier the nerve involvement appears, the more likely it is to become severe. If, however, we exclude the cardio-vascular type the tendency is towards complete recovery. From Table 11. also it is clear that the prognosis is much better once the second week of illness is passed.

The presence of albuminuria in the fourth and fifth weeks must be taken as indicating an attack of more than average severity, and if nerve involvement has not shown itself then, a careful watch must be kept for any nervous sequelae even as late as the seventh week.

In really severe cases of diphtheria it may be a matter of months before the patient quite recovers from the paralysis of the lower limbs and the subsequent weakness of the muscles. After weeks of convalescence in hospital he may still have

a/

a tendency to walk on a broad base, and show traces of an ataxic gait. It may ~~be~~ also be impossible to elicit the knee jerks by the time the patient leaves hospital. (e.g. S.F. Case 3. Table 8.)

Apart from cases of this type the writer has seen no instance of the chronic forms of paralysis which have been described by some observers.

While implication of the pharyngeal or respiratory muscles is in itself a danger, the outlook even then is by no means hopeless. Fortunately these forms of paralysis are of much shorter duration than some of the others and if the patient's strength can be maintained during the period when they are present, there is good hope of his ultimate recovery. In the present series of 1107 cases only eight died of late paralysis.

In the event of the patient recovering from the severe forms of paralysis, one is, therefore, in a position to reassure the parents as to his future physical condition, since it is possible to state with a considerable degree of confidence that the paralysis will disappear completely, and that, after a suitable period of convalescence, he should regain his wonted health and strength.

It is far otherwise, however, when severe symptoms present/

present themselves during the second week. In the present state of our knowledge, "cardio-vascular paralysis" tends to run its course practically unchecked by treatment but in this instance the outlook is distinctly grave.

In no case, in the writer's experience, did recovery take place when "toxic" vomiting had occurred, and the associated signs of the syndrome were well established.

The "latent" period seen in experimental animals is then past and the "poison" absorbed in the early days is carrying out its deadly work. A lethal dose of toxin has apparently been "fixed" out of reach of circulating antibody and even modern methods of treatment are thus of little account.

In spite of all efforts to save him the patient succumbs to a disease which by the insidious nature of its attack has had time to sow the seeds of death even before the victim or his friends are aware of its presence.

It is thus seen that in severe diphtheria there are two critical periods and that these occur approximately in the second and seventh weeks of the disease. In each there is a certain similarity with regard to the effects of treatment, but as far as prognosis is concerned the picture is entirely different. In late paralysis also, we are dealing with a condition which no drug can cure or cut short but here the outlook is good. Always the tendency is towards complete recovery.

Treatment.

There is no specific remedy which will cure or prevent paralysis, and the treatment of the nervous sequelae really resolves itself into the treatment of diphtheria as a whole, excluding the laryngeal form, in which it was found that paralysis never occurred unless there were in addition lesions of the fauces or nasopharynx.

In dicussing the general treatment, which thus includes the prevention of paralysis, the following points call for consideration:-

1. Administration of antitoxin.
2. Prevention of undue exertion on the part of the patient.
3. The supply of suitable nourishment and water.
4. Stimulation by means of cardiac tonics.

1. Administration of antitoxin.

The clinical evidence discussed in Section IV. goes to show that delay in administering antitoxin increases the likelihood of a fatal issue or nervous sequelae.

From experiments on animals Park (31) has shown that, after the injection of more than a lethal dose, the lapse of time increases enormously the amount of antitoxin necessary to prevent death, and after a certain period no amount will avert/

avert a fatal issue.

The first essential in treatment, therefore, is to obtain as soon as possible, a maximum content of antitoxin in the blood. Theoretically this object can best be attained by intravenous injection, but in practice it is often more readily accomplished by giving the serum intramuscularly.

It is now generally accepted that serum exerts no effect when given by mouth or rectum.

The injection of serum subcutaneously is the method most commonly used at the present day, especially in private practice. The disadvantage of this method is that the antitoxin is absorbed comparatively slowly. Experiments conducted by Park showed that, in a healthy man, after subcutaneous injection, the maximum content of antitoxin in the blood was not reached until the third day.

The routine method used by the writer has been by intramuscular injection, the needle being inserted deeply into the muscles on the outer side of the thigh. The injection is no more difficult to carry out than the subcutaneous one, and this method is not contra-indicated even in general practice, where the physician may have little skilled assistance. Large quantities of serum can readily be given in this way, e.g. 12,000 units to a child under five. The main advantage/

advantage, however, of the intramuscular over the subcutaneous route is that the antitoxin is absorbed more quickly, according to Park, twice as quickly; a point which is of vital importance in treatment.

During the year 1921 antitoxin was given intravenously in 40 cases at Plaistow Hospital. Of these 36 recovered and 4 died. Eleven of the recovery cases developed nervous sequelae.

In three cases, two of which were fatal from haemorrhagic diphtheria, the vein was exposed by incision under a general anaesthetic. In all the other cases the antitoxin was given by direct puncture of the vein at the bend of the elbow. The serum was warmed to blood heat without being in any way diluted.

Many of the patients complained of nausea or a feeling of faintness before the injection was completed, and in the majority a severe rigor followed within an hour. In some the rigor lasted for fifteen to twenty minutes and was of such a character as to be alarming, but no fatality resulted. No ill effects persisted, and there was no indication that the usual serum phenomena were more severe. The accompanying Charts Nos. 3. and 4. have been picked out as typical examples of severe reactions following intravenous injection of serum.

The/

TABLE 14.

Analysis of 40 cases of diphtheria treated with antitoxin by intravenous injection to show Paralysis Cases and deaths.

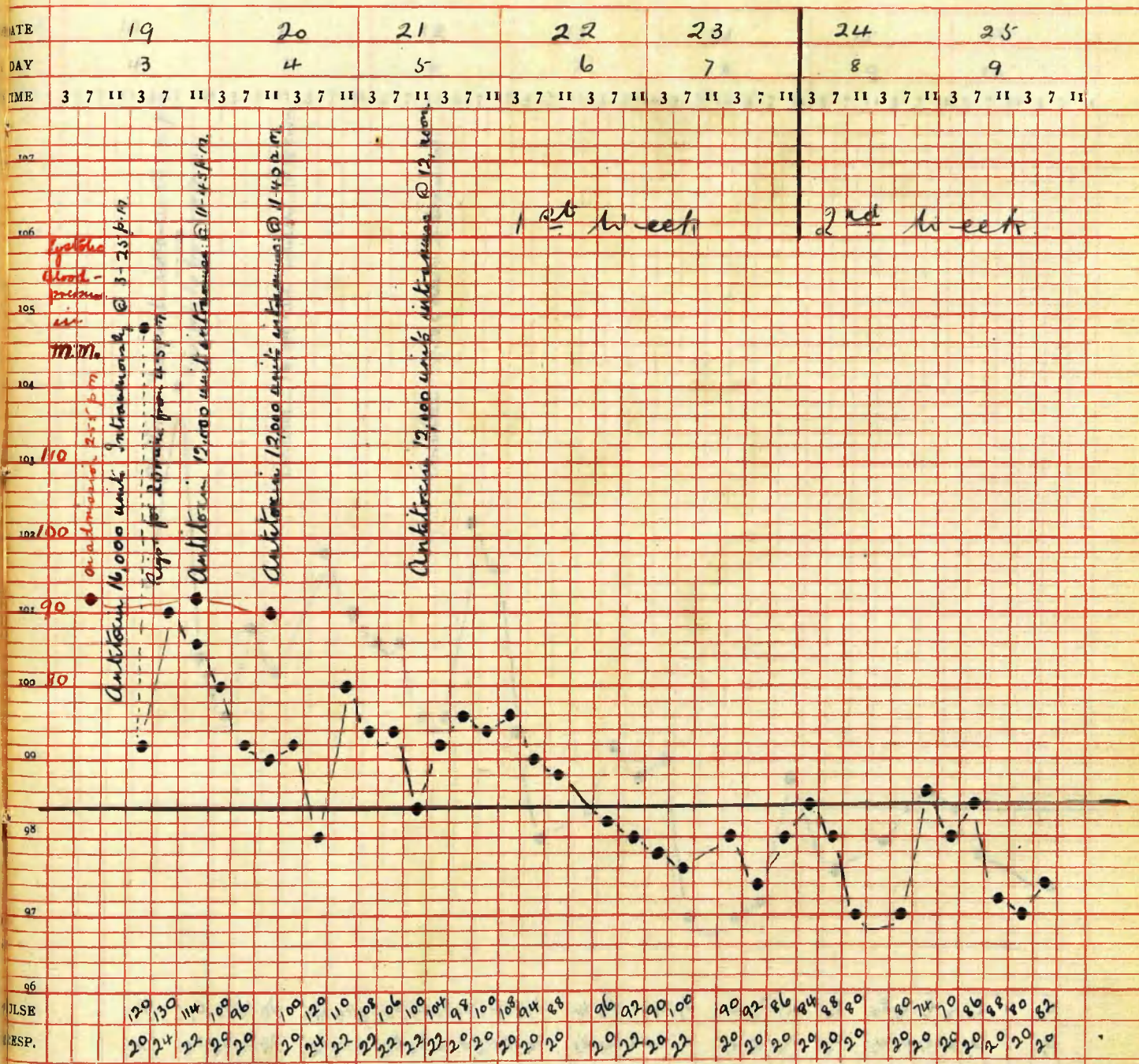
Age Groups.	0 - 5 years	5 - 10 years.	10 - 15 years	Over 15	Total	
Recovery	6	7	6	0	19	Injection given by writer.
Fatal	1	1	-	-	2	
Recovery	*3	7	4	3	17	
Fatal	**1	**1	-	-	2	
	11	16	10	3	40	
	Total Paralysis Cases.					
Recovery	2	5	4	0	11	
Fatal	-	1	-	-	1	

* 1 Recovery Case open operation under chloroform anaesthesia

** 2 Fatal cases " " " " "

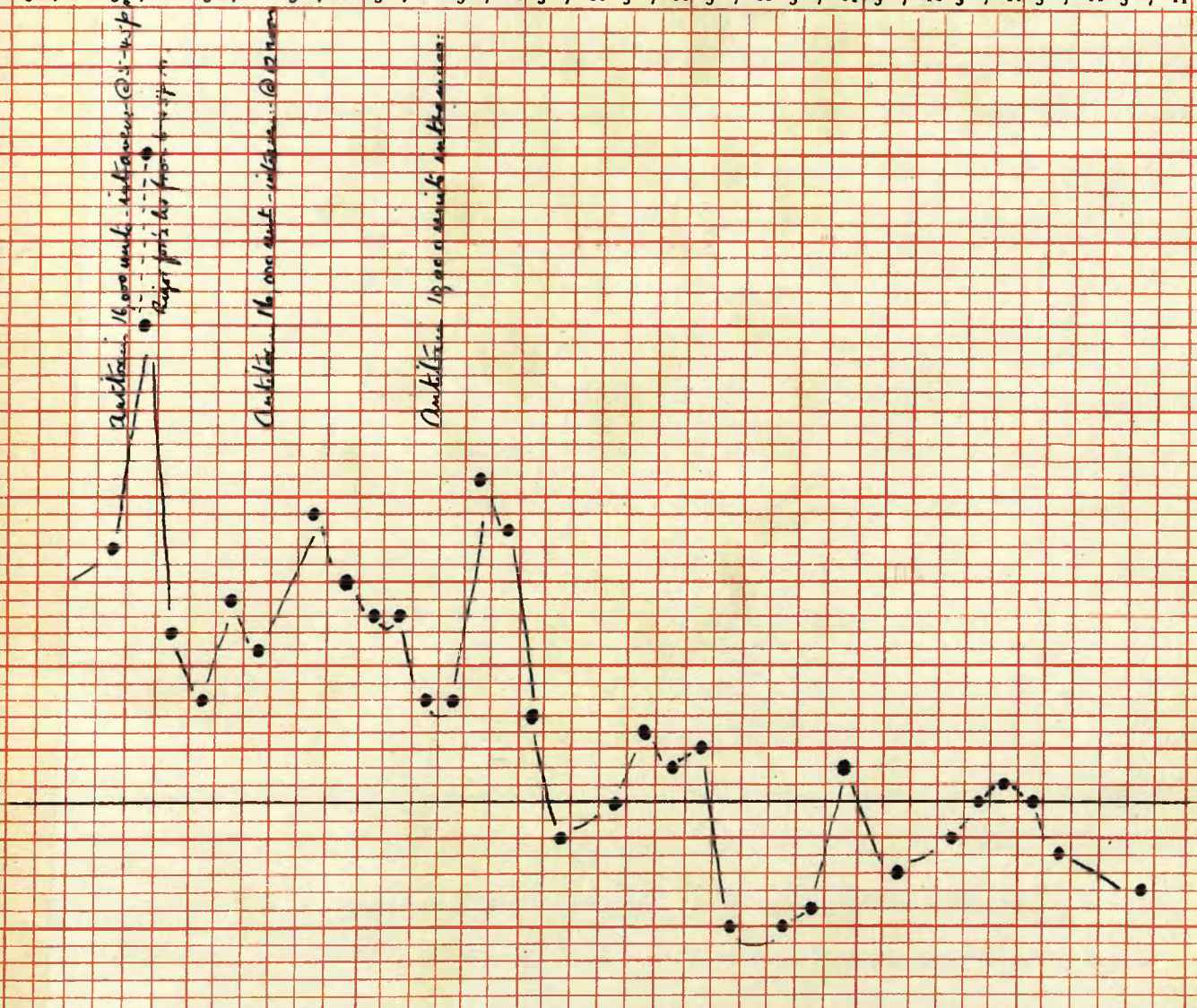
Chart

No. 3. Name M. J. Aged 11 years. F



Chart

10.4. Name J. B. Aged 15 years. M.



The disadvantages of this method are that in young children the injection may be difficult or impossible to carry out, and in advanced "toxic" cases there may be an actual collapse of the veins. The latter condition was present in the patients on whom a cutting operation was performed and the vein exposed.

The writer's general impression is that the method is of value. The cases which were treated by intravenous injection were selected because of the severity of the disease or the lateness in receiving serum. These cases occurred after he had a fair experience of diphtheria, and were such as would be likely to show signs of nerve involvement at a later period of the attack.

In many, no nervous sequelae developed, however, whilst in others,(e.g. Cases 3 & 4. Table 9.) the nerve involvement was not so severe as was anticipated from the appearance of the local lesion and the course taken by the disease during the first few days of the patient's stay in hospital.

The subject of Anaphylaxis is outside the scope of the thesis,but it is interesting to note that only in one case, out of the many hundreds who were admitted to Plaistow Hospital since July 1919, has the writer seen an immediate reaction after a first injection of serum. This patient quickly recovered and there were no bad after effects.

Twenty-five cases received a second injection of serum after an interval varying from eighteen days up to many months. In no instance was there a fatal result and only in one case was there a severe reaction with collapse and subnormal temperature. This occurred four hours after the injection.

In the writer's opinion, there need be no hesitation in giving antitoxin, should circumstances demand it, even although the patient has had serum previously. It has been his practice in such cases to give a small testing dose (2000 units) and if no reaction occur within 6 hours, the necessary doses for treatment are then given as if the patient were receiving serum for the first time.

With regard to the dosage of serum required it is difficult to lay down stereotyped rules. Many factors have to be taken into account, such as, the situation and extent of the local lesion, the accompanying adenitis, the day of illness on which the patient comes under treatment, and the rapidity with which the membrane disintegrates. On the other hand, it must be remembered that a patient may have comparatively little membrane and yet be distinctly "toxic".

The dosage of serum advocated by different leading authorities varies enormously. The difficulty appears to be in estimating when sufficient antitoxin has been given to neutralize/

neutralize the toxin absorbed from the local lesion, and this is a point which has to be decided by the clinician in each individual case.

Ker favours the method of divided doses, given at intervals of twelve to twenty-four hours, and begins with comparatively small amounts. He admits, however, that some cases may require 40,000 units but has never given more than 64,000 units.

Park, on the other hand, advocates the single large dose, and holds that to exceed 25,000 units in a child and 50,000 in an adult is useless and unnecessary. (27)

It has been the writer's practice to estimate the initial dose on the factors stated above. Repeated doses are then given at intervals of twelve to twenty-four hours, the number depending on the rapidity with which the membrane breaks up.

The following is a scheme of the approximate dosage which he has been giving at Plaistow Hospital:-

		Units.
Group I.	Both tonsils well covered with membrane	24,000 - 30,000
" II.	2 T + Uvula	up to 36,000
" III.	2 T + U + Palate	" " 40,000
" IV.	2 T + U + P + nasal discharge	" " 50,000

In Group IV. the initial dose would be 16,000 - 20,000 units.

These doses are higher than the writer was accustomed to/

to give in 1914-15 when he had the privilege of working under the late Dr. Biernacki. During the epidemic, however, there seemed to be an increased virulence in the type of diphtheria and many very severe cases came under treatment. From time to time attempts were made to reduce dosage but this was not found to be practicable or advisable, and when severe cases have presented themselves since the epidemic, these figures have actually been exceeded. While small doses are useful and efficient if given early in mild cases it is otherwise with very severe cases seen late. Further, if there be any clinical value in the theory of displacing "fixed" toxin by massive doses of antibody large doses of serum must be administered. On the other hand if the membrane is disappearing when the patient comes under treatment, even large amounts of serum seem to be useless.

2. Prevention of undue exertion.

When we consider the great physical prostration which is associated with severe diphtheria and the tendency to circulatory failurs which develops in the early weeks of the disease, it is clear that every effort must be made from the outset to husband the patient's strength and prevent any exertion which would throw undue strain on the heart muscle. In/

In all but the mildest cases the patient should be kept in bed for three weeks but in severe cases this period should be extended to six weeks, and even then he is only allowed up if there is no paralysis present.

As regards local treatment, all that is necessary is syringing with weak boric lotion every four hours to wash away any discharges and thus promote healing of the local lesion.

At Plaistow Hospital, aperients are not given to severe cases in the early stages as they may cause vomiting. The bowels are relieved by enemata and these are continued in paralysis cases until the patient is convalescent.

During the first fortnight the patient is kept on light diet, and while membrane is present on the fauces fluids only are allowed. In the absence of nausea or vomiting a liberal diet is given as soon as possible, since, if severe paralysis ensues, the patient may require all his strength to carry him through the attack.

As a satisfactory excretion of urine is important in severe cases, water is allowed ad libitum in addition to the feeds and a daily record is kept of the amount of urine passed in the twenty-four hours.

Vomiting at the onset of the disease, as a rule, has no grave significance, but it is otherwise at the beginning of the/

the second week, especially if it is associated with signs of failing circulation. While vomiting in itself does not constitute the real danger, it certainly is responsible for much extra exertion on the part of the patient, who in addition is deprived of nourishment and water. In practically all severe cases it may herald the onset of grave symptoms. When it occurs the diet is restricted to fluids only. If milk diluted with water is not tolerated, peptonized milk or whey is given. When, however, the vomiting is persistent, it will be necessary to stop all feeds by mouth and institute rectal feeding.

Intracellular salines may be tried where the vomiting cannot be controlled and rectal feeds or salines are returned. They were given by the writer only in cases which proved fatal and he is unable to say that he has seen any benefit from their use.

Treatment of Paralysis.

Paralysis in diphtheria is generally partial, and when the patient is lying quietly in bed, the mild forms may escape notice. It would appear that exertion however brings out and accentuates any nerve involvement that may be present. Thus it occasionally happens that a patient who has shown no sign of nerve lesion while in bed develops definite paralysis after/

after being allowed up. (e.g. Case 5. Table 9.) In these cases there is always a risk that fatal syncope may occur at any moment, or short of that, acute arrhythmia with severe cardiac embarrassment. It is in view of this contingency that stress is laid on the necessity of keeping diphtheria cases in bed until the risk of paralysis is past.

When the patient has survived the danger of early circulatory failure, there is often a lull or quiescent period during the third and fourth weeks, when he appears to be convalescent and out of danger. It is frequently in the fifth week that the severe forms of paralysis make their first appearance, and by extending rapidly may cause serious risk to life.

When the palatal paralysis is slight, or the nerve involvement affects such parts as the lower limbs, the eyes and the muscles of the neck, all the treatment required is complete rest in bed, careful dieting and attention to the bowels.

When the soft palate is affected to such an extent as to cause regurgitation nasal feeding should be commenced. If salivation is present from implication of the pharyngeal muscles, the foot of the bed should be raised on blocks, and it may be necessary to have recourse to rectal feeding.

When paralysis extends to the respiratory muscles, there will/

will usually be some circulatory embarrassment as shown by rapidity and irregularity of the pulse. The cardiac tonics to be mentioned presently are then indicated. A cylinder of oxygen should also be kept constantly at the bedside and the gas freely administered if any respiratory embarrassment occur.

When it is borne in mind that the severe forms of paralysis are of comparatively short duration, no means of treatment should be left untried which will help in maintaining the patient's strength. The tendency is towards complete recovery but while the diaphragm and pharyngeal muscles are paralysed, he is in constant danger of suffocation or a fatal syncopal attack, and for days his life may be hanging by a thread. In recovery cases when these severe forms have passed off there is a tendency to tachycardia and prolonged rest in bed is necessary until the pulse returns to normal. No relapses of the paralytic phenomena occur, however, and convalescence although it may be slow is, in most instances, quite uneventful.

Having dealt with the therapeutic measures employed during the stage of late paralysis, the writer wishes next to consider the treatment of circulatory failure in the early weeks of the disease.

In cases where "cardio-vascular paralysis" was threatening he relied mainly on Camphor (Curschmann's Solution), whisky and adrenalin (1-1000). In some of the cases he administered the/

the latter drug before signs of failing circulation appeared, with the object of overcoming any adrenalin insufficiency which might be present, and to avoid sudden raising of the blood pressure when the heart was actually failing. He cannot say, however, that any definite improvement resulted from this line of treatment. The usual dose of adrenalin solution for children was five minims injected intramuscularly every four hours. Camphor Solution was administered in the same way in five minim doses. Whisky as a stimulant was given to children in doses of one or two drachms by mouth every four hours, or in rectal feeds two to four drachms every six hours.

One other drug must be mentioned before leaving the subject of cardiac tonics, namely strychnine. This drug has a wide reputation for its effect in diphtheritic paralysis but it has no specific action. It is a good general tonic and has been used by the writer for that purpose in considerable doses during the stage of late paralysis. It was never given in the early circulatory failure of the disease for fear of overloading or flogging into unnecessary action an already failing heart. While testing this drug one sixtieth of a grain was given every six hours for six days at a time, even to children under five, without symptoms of poisoning. The effect was carefully watched but no marked benefit was observed from its use.

In/

In severe diphtheria the lowered blood pressure no doubt allows the myocardium to do its work more easily. It is, therefore, doubtful if powerful stimulation and raising of the blood pressure against a failing heart is judicious treatment. A great deal can be done to assist the circulation by raising the foot of the bed on blocks to ensure an adequate supply of blood to the vital centres, and by the administration of oxygen for five or ten minutes every hour. It is also essential that the patient be kept warm not by heaping on bedclothes but by hot water bottles and relays of warmed blankets. These measures are, in the writer's opinion, of more value than artificial stimulation by means of drugs. In no other disease, in his experience, is nursing of such vital importance as in the critical periods of grave diphtheria, whether in the early or late stages of the disease. The severe cases described in the thesis were certainly brought back to health only by the unremitting care and attention of a skilled nursing staff.

SECTION VI.

Conclusion.

Conclusion.

Fortunately many cases of diphtheria with nerve involvement do recover, but when a certain amount of "poison" has been absorbed, even modern therapeutic measures are powerless to save the patient. Treatment by itself, therefore, is not sufficient, and the real objective must be prevention.

There are two methods of preventing diphtheritic paralysis. The first - and this is open to us - is early diagnosis and early treatment with antitoxin. The incidence of diphtheria is greatest and the mortality highest in the first five years of life, and in children of that age a diagnosis of "ulcerated throat" should always be looked on with suspicion. If the condition turn out to be diphtheria and there has been delay in giving specific serum, the results too often are disastrous. It is very rare for cases treated on the first day to develop serious symptoms. In the writer's experience, it is the late cases which develop paralysis and the late cases which die. During periods of epidemic prevalence at least, the sequence of/

of diagnosis and treatment might well be reversed, and serum administered before an absolute diagnosis is made.

The other method - and the ideal one - is to prevent diphtheria. Within recent years hopes have been raised that this may be realized by means of the Schick test and inoculation of susceptibles with toxin-antitoxin mixture. (27, 31, 32). It is too soon to estimate the true value of this method of artificial immunization, but the results so far have been encouraging. Further investigation, however, is necessary to ascertain if the application of these measures on a large scale is practicable or advisable, and at the moment there seems no immediate likelihood of diphtheria being added to the list of diseases which have already yielded to the efforts of preventive medicine.

SECTION VII.

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