OBSERVATIONS ON THE CARDIO VASCULAR COMPLICATIONS OF DIPHTHERIA.

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Diphtheria is one of the acute infectious diseases which displays a marked liability to affect the cardio vascular system. It is, of course, characteristic of almost all acute fevers that the heart is involved pari passu with the intensity of the disease process. Enteric fever and Malaria are notable examples. Acute rheumatic fever involves the heart to a marked degree, and may be placed with diphtheria as a disease in which the involvement of the heart is strikingly prominent. In other acute fevers there is usually some dilata-:tion of the heart, as indicated by an enlargement of the area of deep cardiac dullness, with possibly a soft systolic murmur at the apex; the pulse may be soft and compressible. A Post Mortem examination may show a heart with pale muscle substance with, microscopically, fatty or granular degeneration of the muscle fibres. In scarlet fever of the more severe types, and particularly in septic cases, the heart is affected more often than is usually recorded. I have reason to affirm this, after having/

having observed cases of scarlet fever shewing a pulse persistently rapid in spite of an almost normal temperature, along with a slight increase in size of the area of cardiac dullness.

In Diphtheria, however, the involvement of the cardio vascular system may be so grave and serious in its consequences that it becomes a complication to be watched for with grave anxiety, and if possible warded off by every possible means. Indeed, it may be laid down as an axiom in the treatment of diphtheria; that once the initial dosage with antitoxin has been carried out to the extent considered necessary, the remainder of the treatment is directed against any possible affection of the cardio vascular system by the diphtheria toxin.

Before proceeding further, it will be advisable to explain that the expression "Cardio vascular system" is employed owing to the divergence of opinion as to the actual pathological condition present in diphtheria, causing the profound depres-:sion of the heart and circulatory system so characteristic/

characteristic of the disease; this question will be studied more fully later in this thesis.

Diphtheria, to the average person, is a disease in which the chief danger lies in respiratory embarrassment as a result of the implication of the air passages. It is also associated with a possible operative interference becoming essential to relieve the patient of this obstruction to breathing. No doubt this may be looked upon as a tradition handed down from the days when such incidents marked the usual course of the malady, before the introduction of antitoxin in treatment tended to check the spread of diphtheritic membrane from the fauces to the larynx and trachea.

Bretonneau,[1] writing in 1826, regarded the danger of asphyxia as the chief trouble in diphtheria, though one of the cases described by him (P. 23) would appear to be a case in which death resulted from toxaemia acting on the cardio vascular system.

Trousseau[2] also considers the malady from much the same standpoint.

Perhaps/

Perhaps an explanation of the usual termination of a case of diphtheria a hundred years ago may be found in the fact that death occurred from mechanical means. The false membrane implicated the air passages and caused asphyxia, with perhaps some diphtheritic broncho pneumonia. There was no specific treatment, such as is now afforded by antitoxin, to prevent the extension of false membrane. The patients did not, as a general rule, live long enough to display signs of circulatory failure outweighing in their gravity the initial pathological process. Morell Mackenzie[3], writing in 1878, says: "By far the larger proportion of fatal cases terminate by gradual apnoea, but a certain percentage sink from asthenia, blood poisoning, and cardiac thrombosis." At that time, therefore, it was recognised that circulatory failure was responsible for a proportion of deaths from diphtheria, though laryngeal and tracheal obstruction was still considered to be a more usual cause of a fatal termination. In describing/

describing the course of typical diphtheria he draws attention to the fact (p.28) that in the third stage there is the danger of signs of heart-failure appearing, and that the patient may die of syncope.

Jenner (Lectures and Essays on Fever and Diphtheria; 1893, p.512) describes an asthenic form of diphtheria in which the patient succumbs in ten or twelve days, and states: "it is failure of the heart's action and not want of breath that causes death."

At the present day diphtheria may be regarded as a sapraemia. The local lesion in the throat, with, in more severe cases, the addition of the naso pharynx, elaborates toxins which are absorbed into the blood stream rapidly, in view of the rich lymphatic supply of these regions. Hence, it is not surprising that the cardio vascular system may receive damage which proves fatal to the patient. The administration of antitoxin prevents the spread of/

of diphtheritic membrane, but enough toxin may have been absorbed to cause serious effects. Thus may be found the explanation for the fact that the longer the duration of the disease before antitoxin is given, the greater is the liability of the cardio vascular system becoming implicated, and, of course, the greater is the liability to the various paralyses of nerves, which may be sequelae of diphtheria. It may also be noted that cases of laryngeal and tracheal diphtheria rarely shew circulatory failure or paralyses, owing to their less abundant lymphatic supply, as compared with the throat and naso pharynx.

The modern view of the risks attendant upon diphtheria is well made out by Claude B. Ker[4] in his statement that: "if we exclude broncho pneumonia, which is in laryngeal cases a common cause of death, circulatory failure is undoubtedly responsible for the greatest number of deaths in diphtheria."

During a period of six months as resident Medical Officer at Edinburgh City Hospital, I have taken/

taken the opportunity of observing a considerable number of cases of diphtheria.

During the period - Jan 1st to June 30th - 659 cases were admitted as diphtheria. Of this number 55 cases were contacts or carriers, and in 50 cases the diagnosis was proved to be some other condition; that is to say, 554 cases were clinical diphtheria.

Of this number, 35 died. Deducting one case with concurrent measles, and one case who developed acute appendicitis and who died as a direct result of that, and not of diphtheria, the correct mortality is 33, giving a case mortality of 5.9 per cent. Including carriers and contacts, who were admitted owing to diphtheria bacilli having been found on examination of throat swabs, the case mortality is 5.4 per cent.

Out of the total of 33 deaths, 9 deaths were of laryngeal cases, the other 24 deaths being all due to the effect of diphtheria toxins in the cardio vascular system, as distinct from the effect of/

of diphtheria upon the respiratory system.

Of the nine laryngeal deaths, one had the operation of tracheotomy performed owing to impending asphyxia. The operation was perfectly successful in relieving the dyspnoea, but on the evening of the day succeeding the operation, symptoms of cardio vascular weakness developed; death was directly due to this and not to any respiratory condition. Including this case in the series of deaths from cardio vascular depression, one has a total of 25 out of 33 deaths as a result of this condition, a percentage of 75.8.

In addition to the fatal cases of cardio vascular failure, I have made observations of 18 other cases of diphtheria in which signs of circulatory depression were distinct. This does not convey a true idea of the prevalence of such a condition, for a very large number of cases of diphtheria will be found to display signs of more or less depression of the circulatory system, as evinced by a persistently feeble and soft pulse, pallid/

pallid complexion, with maybe a tendency to cyanosis of cheeks, lips, and some enlargement of the area of deep cardiac dullness.

If one were to make an arbitrary standard of the extent of diphtheria, by taking the dosage of antitoxin as such standard, a case requiring 40000 units may be regarded as an average one, according to Claude B. Ker ; anything over 8000 units represents a serious case. On observation of a number of average cases, one would not fail to be struck by the large number displaying the above mentioned signs for a greater or less period of time. On coming to the serious cases, it would be found that almost all without exception present these signs: if not on admission to hospital, then in the first few days. In some of the milder cases the patient may appear to be fairly well, and may be with difficulty restrained from sitting up in bed, but the pulse will be found to be weak and soft - out of all proportion to the patient's general appearance.

ETIOLOGY.

It is a difficult question to predict which cases of diphtheria will develop cardio vascular failure, and it is impossible to say which cases will give us cause for anxiety. Indeed it cannot be too strongly asserted that any case of diphtheria may develop serious or even fatal cardio vascular failure, the "cardiac paralysis" of some writers.

There can be little doubt that the length of time elapsed between the commencement of the illness and the first administration of a dose of antitoxin bears a direct ratio to the chances of a fatal result from circulatory failure. All the time the diphtheritic membrane is spreading, more and more toxin is being manufactured and absorbed readily into the circulation by means of the abundant lymphatic supply of the throat and naso pharynx. Moreover, by the time that antitoxin is administered, the prospects of its exercising a specific action are considerably diminished, the toxin having become fixed in the body tissues where/

where it is neutralised only with difficulty.

There is another aspect of the late case which merits consideration. If the case is seen for the first time after some days have elapsed since the beginning of the diphtheritic process, there is the possibility that the local condition of the throat may have improved spontaneously, and a dose of antitoxin may be given commensurate with the state of the local lesion as then seen, and not as it was, say, two or three days previously. Thereby, an insufficient amount of antitoxin is given to combat the real extent of the disease.

It goes without saying that the intensity of an attack of diphtheria, as indicated by our arbitrary standard of the amount of antitoxin necessary, is a factor in the possible causation of cardio vascular trouble. The greater the intensity and extent of the disease, the greater is the prospect of toxin being absorbed in sufficient amount to cause serious results.

The site of the diphtheritic process is of considerable importance as a factor in the causation of/

of cardio vascular trouble. The existence of diphtheritic membrane in the naso pharynx, as shewn by a purulent nasal discharge, vastly increases the possibility of death from circulatory failure. It must be admitted, of course, that implication of the naso pharynx usually means a case of diphtheria of far more than average severity. It is noteworthy that of this series of cases, 15 out of the fatal ones had nasal diphtheria in addition to faucial. Out of the total of 554 cases between Jan. 1st and June 30th, 62 cases had nasal diphtheria either alone or in addition to faucial diphtheria. The case mortality rises to 24.2 per cent when the nasal region has sustained a diphtheritic infection.

In laryngeal cases, on the other hand, death from cardio vascular trouble is rare. The danger in them is from asphyxia or broncho pneumonia. The first may be prevented by the prompt administration of antitoxin in adequate quantity, use of a steam tent or other means of impregnating the/

the air with steam, or if these measures fail, intubation or tracheotomy. There is a considerable tendency to broncho pneumonia in intubation and tracheotomy cases, but if they escape this danger they usually make a good recovery. The case I have described previously forms a notable exception, and was the only laryngeal case where death was directly due to circulatory failure and not to any respiratory complication during the six months named.

It is noted by Claude B. Ker[5] that laryngeal cases rarely develop any of the paralyses which are more liable to occur after faucial diphtheria and still more often, nasal diphtheria.

There is the question of the liability of cardio vascular trouble consequent upon other paralyses. The most dangerous of these is a palate paralysis, and particularly when it appears early in the course of the disease. Seven of the series of cases developed palate paralysis.

Such symptoms as albuminuria, haemorrhages from/

from nose or mouth, petechial haemorrhages under the skin, or bruising at sites of hypodermic injections are all indicative of a grave danger of cardio vascular failure, just as they are indicative of a very severe type of diphtheria.

Table showing day of disease on which case came under treatment.

Fatal cases		Non fatal cases.	
2nd day	2	2nd day	4
3rd day	4	3rd day	5
4th day	7	4th day	5
5th to 7th day	12	5th to 7th day	4

As none of the cases was seen until admission to hospital, reliance had to be placed on statements made to the ambulance staff concerning the duration of the disease. It is therefore quite possible that some cases had been ill longer than was stated, the throat condition not being observed by parents in its early stages.

Amounts of Antitoxin given.

	fatal	non fatal.
Under 8000 units	2	11
8000 to 16000 units	12	4
16000 to 24000 units	6	3
Over 24000 units	5	0

PATHOLOGY.

The pathology of diphtheria presents features in common with other infectious diseases. Myocardial degeneration is commonly found. As regards the features with which this thesis is concerned, there is considerable diversity of opinion.

Hibbard[6] gives accounts of larger numbers of cases in which degeneration of the vagus nerves was found.

Bolton[7] considers that in diphtheria there is an acute degeneration of cellular elements in the medulla, due to the action of diphtheria toxins on the nerve cells; he found no signs of any degeneration of the vagus.

Sergent[8] found that in many cases of infectious disease, including diphtheria, there were haemorrhages in the medulla of the suprarenals, and advances the opinion that suprarenal insufficiency occurs in diphtheria. His observed train of symptoms "L'abbattement et la prostration avec hypothermic petitesse du souls, tendence du collapsus" are/

are to be found in all cases of diphtheria in which death results from failure of the circulatory system.

A recent work by M. Esther Harding[9] brings forward interesting information as to the pathology of this condition. She found that in diphtheria there was marked cardiac degeneration accompanied by Oligaemia, i.e. a deficiency in the volume of the blood in circulation; this may be either quantitative or distributive. She also found an increase in the specific gravity of the blood, ranging up to 1060 or 1062, as compared with the specific gravity of 1040 to 1045 of normal children, and describes a condition in which there is an increased transudation of lymph from the blood to the tissues, to which is applied the term "lymph-logging". She considers that there is a stasis of blood in the peripheral circulation and capillaries analogous to that described in shock (by the Special Investigation Committee on Surgical Shock and Allied Conditions[10]).

It is thus evident that a great many conditions may participate in the train of symptoms found in the cardio vascular failure of diphtheria.

SYMPTOMS.

To study the cardio vascular symptoms of diphtheria it is advisable to start with a brief account of the malady.

According to Gee: "The first result of diphtheria infection is local. ..... Infection of deeper organs and of the whole body is chiefly due to absorption of soluble venom from the place where the growth of microbes is proceeding."

Diphtheria may be simple, or malignant; the former's chief character is the local affection; in the latter there is varying degree of toxaemia.

There is nothing specially distinctive of the prodromal period. The patient, usually a child, may complain of generalised pains, headache, lassitude and even vomiting. Actual fever is not a symptom of great importance, though frequently the temperature may be elevated for a day or two at the onset of the disease; later, the temperature rarely goes above normal and is very often subnormal.

Sore throat is usually the first sign of local trouble, but may cause little discomfort until membrane/

membrane is formed. There may also be symptoms of implication of naso pharynx - coryza, mouth breathing.

Glands.

The glands at the angles of jaw are usually somewhat enlarged and tender; marked enlargement may indicate an infection of the throat with other organisms than diphtheria.

Throat.

If the throat be seen before diphtheritic membrane has had time to form, it will be found to be congested and swollen. A point in favour of diagnosis of a diphtheritic throat is that the patient seldom complains of any pain or difficulty in opening the mouth, as in acute tonsillitis and mumps.

Formation of false membrane begins as one or more whitish specks, usually on the tonsil or uvula. Quite commonly one side only is affected, a point of some importance in the distinction from other affections of the throat.

These coalesce to form a membranous patch of whitish/

whitish, or yellowish white appearance, at first thin, later, thick and opaque.

This membrane is very frequently strongly adherent to the mucous membrane beneath, and if it be removed, a raw, bleeding surface is left, upon which membrane re-forms.

When the case is not seen until four or five days after its commencement, the diphtheritic membrane may by that time have undergone decomposition, resulting in a foul putrid odour of the breath.

There is a variable amount of swelling of the tonsils and uvula; in some cases it may be slight; in others, usually the severer type of case, the tonsils and uvula may be so swollen that only a narrow gap is left between them.

As a general rule, therefore, the patient, when first brought under observation, attracts attention more because of the local condition from which he is suffering, than from the general symptoms. In a severe case of diphtheria, where there is an extensive amount of false membrane, it/

it is often striking to observe the "toxic" appearance of the patient - pallor, considerable prostration and lassitude, with a soft, compressible pulse.

Cases which give trouble owing to symptoms of implication of the cardio vascular system may be considered from the point of view of an "early" type and a "late" type. (Claude B. Ker. p.399)[12]

The following case may be taken as an example of the early occurrence of failure of the cardio vascular system.

E. C. age 7, female.

Taken ill on 26.1.20 with headache and vomiting.

On 28.1.20, complained of sore throat, with enlargement of glands of neck at angle of jaw.

29.1.20. Admitted to Edinburgh City Hospital.

Throat congested, with swelling and enlargement of both tonsils. False membrane covering both tonsils. Glands of neck at angle of jaw enlarged and tender.

Heart sounds regular and closed.

Lungs healthy.

6000 units antitoxin given.

30.1.20. Other 6000 units antitoxin given.

31.1.20. Vomited twice. Pulse soft and feeble - 90 per minute.

Heart sounds fairly strong in character and closed. No enlargement of area of cardiac dullness.

Epistaxis in the morning. Albuminuria present.

1.2.20. Condition much the same.

2.2.20. Cardiac dullness extends 1½ inches to the right of mid sternal line. Haematemesis in evening. Very restless. Given Morphia gr.$\frac{1}{12}$, Atropine gr.$\frac{1}{300}$

3.3.20. Character of heart sounds fairly good. First sound well heard. Liver dullness increased: extends one inch below costal margin in nipple line.

4.2.20. Pulse weaker - 140 per minute. Extremities cold and pale.

Heart sounds audible with difficulty.

Died at 9 p.m.

This case was one of more than average severity, and was not admitted to hospital until the fourth day.

On the third day in hospital the patient vomited/

vomited twice; the pulse was soft and feeble, the heart sounds regular and closed, and no enlargement of the area of cardiac dullness.

Vomiting in a case of diphtheria should be regarded as a sign of impending trouble: unless some very obvious cause can be found to account for it. The first that suggests itself is indiscretion in diet. In the City Hospital, however, all diphtheria patients are placed on a fluid diet - milk, a little Bengers Food, etc.- which is cauticusly added to well after the throat condition has entirely cleared up. Hence, any attack of vomiting early in the course of the disease is to be regarded with suspicion.

It may appear strange that vomiting should be considered one of the cardinal signs of failure of the circulatory system in diphtheria.
Hibbard[13] attributes it to a degeneration of the vagi as a result of the action of diphtheria toxin.
When one considers that both the heart and the stomach are supplied with nerve fibres from the two vagus nerves, such an explanation seems feasible.

A weak, soft, and compressible pulse forms another indication of impending cardio vascular failure/

failure in diphtheria.

In scarlet fever and measles, the pulse is usually found to be of good volume, and increased in rate; in the case of scarlet fever the increase in rate is rather more than in proportion to the rise of temperature.

In diphtheria, on the other hand, the pulse in the early days of the disease is not specially disturbed as regards rate, but it is usually considerably weaker than would be expected from the general condition of the case and the temperature. The temperature in diphtheria, one may note, is of little importance as an index of the gravity of the disease. A normal temperature does not necessarily indicate that the patient is progressing favourably; frequently it remains subnormal.

Hence, there is more reason to be surprised when a weak pulse is found in spite of a normal temperature and is a warning to be on guard for circulatory trouble.

The diphtheria patient with a failing cardio vascular system may be said to have a distinctive facies./

facies. The forehead and cheeks have a most noticeable waxen pallor which is in striking contrast with the redness of the lips, in cases where the failure is slight. When the failure is more marked, and advancing, the colour of the lips assumes a cyanotic tinge.

The hands and feet are cold and clammy owing to the defective circulation.

A feeling of discomfort or even actual pain in the praecordial area may be complained of by the patient.

Another type of cardic vascular trouble manifests itself later in the course of the disease. Generally the case has been one of more than average severity, and the pulse of poor quality all along. There may in addition have occurred a paralysis of the palate, resulting in regurgitation of fluids down the nose and a nasal quality of voice.

The following case is an example..

W. F. male, aet. 8 years.
Admitted to Edinburgh City Hospital on 18.4.20 on 2nd day of disease.

Membrane on tonsils and uvula, also posterior pharyngeal wall.

Glands/

Glands of neck at angle of jaw somewhat enlarged and tender.

Heart sounds closed and regular.

Pulse soft, rate 100 per minute.

8000 units antitoxin given intramuscularly.

19.4.20 8000 units antitoxin at 8 a.m.

8000 units antitoxin at 8.45 p.m.

22.4.20. Morbilliform serum rash.

23.4.20 Haemorrhagic spots on neck and chest.

27.4.20 Developed paralysis of palate with regurgitation of fluids.

Pulse soft. Rate 120 per minute.

Albuminuria present.

29.4.20. Vomited twice.

30.4.20. Auscultation of heart reveals extra systoles, occurring in sequence of threes, also singly.

Area of cardiac dullness slightly increased - 1½ inches to right of mid sternal line and ½ inch to left of nipple.

5.5.20. Pulse still soft and weak. Rate 130 per minute.

10.5.20. Paralysis of diaphragm now present, causing marked cyanosis and dyspnoea. Pulse almost imperceptible.

Death at 12.45 a.m. 14.5.20.

In this case there is the added danger of subcutaneous haemorrhage. This is frequently met with in malignant cases and indicates an invariably fatal result.

The addition of paralysis of the diaphragm only serves to increase the handicap under which the weakened heart is labouring, by causing imperfect oxygenation of the blood and impaired nutriment of the heart muscle.

It has already been mentioned that in cases of laryngeal diphtheria, death from "cardiac paralysis" is uncommon if the obstruction to respiration has been overcome either by intubation or tracheotomy, or in less grave cases, steam inhalation.

The following case is a noteworthy exception.-

J. S. male, aet. 6½ years.
Admitted to Edinburgh City Hospital on 7th day of disease. (11.6.20)

Croupy cough on 10.6.20.

Membrane on both tonsils.

Glands of neck enlarged.

Heart/

Heart sounds closed and regular.

Pulse of good volume; rate 100 per minute.

8000 units antitoxin injected intramuscularly.

12.6.20. Still croupy. Hoarseness of voice. Indrawing of epigastrium on inspiration.

2 p.m. Marked dyspnoea.

Tracheotomy performed. Large membranous coat of trachea coughed out of opening into trachea. Tube inserted.

8000 units antitoxin given, and a similar dose at midnight.

13.6.20. Breathing easily through tube. More membrane coughed up.

Vomited once. Pulse rather weak.

14.6.20. Pulse became very weak; rate 120 per minute. Face pale; hands and feet cold.

Heart sounds closed and regular.

Tendency to haemorrhage and bruising at site of injections.

Restless during the night.

2 p.m. Heart sounds very rapid - 180 per minute. Cardiac dullness 2 inches to right of middle line. Bruit de galop present.

Liver dullnessextends 1 inch below costal margin in nipple line.

Death at 3 p.m.

In the above case, there was, it must be admitted some faucial diphtheria present, but this was overshadowed by the graver symptoms of laryngeal diphtheria, which rendered necessary the performance of tracheotomy.

It is also to be noted that the patient did not come under treatment until the seventh day of the disease, a fact which can surely be regarded as contributory to a possibility of complications due to absorption of toxins.

The cases quoted hitherto have been those in which a fatal termination has resulted, but nevertheless others occur in which the cardio vascular system presents signs of disturbance, which, however, may not progress far enough to cause death.

These more favourable cases may be due to.-

(a) insufficient absorption of diphtheria toxin;

(b) early administration of antitoxin in adequate amounts, thereby neutralising to a large extent whatever toxin may have been absorbed.

(c)/

(c) the powers of resistance of the patient to diphtheritic toxin.

The following case affords an example of disturbance to the cardic vascular system.

H. McD. aet. 12, female.

25.2.20. Admitted to Edinburgh City Hospital in 4th day of disease.

Membrane on both tonsils, uvula, and left anterior faucial pillar.

Glands at angle of jaw enlarged and slightly tender.

Heart sounds closed and regular.

Pulse of fair volume; rate 96 per minute.

8000 units antitoxin injected intramuscularly at noon, and repeated at midnight.

7.3.20. Pulse weak and of low pressure. Rate 90 per minute.

Heart sounds regular. Slight prolongation and roughening of first sound in initial area.

Right border of cardiac dullness 1½ inches from midsternal line.

Left border ½ inch external to nipple.

29.3.20. Systolic murmur at apex and base; rough first sound.

1.4.20. Occasional extra systoles audible on auscultation.

5.4.20. Vomited several times.

No change in pulse or cardiac signs.

15.4.20. Pulse still rather weak; extra systoles still present.

15.5.20. Allowed out of bed.

29.5.20. Auscultation for prolonged interval shews only one or two extra systoles. No enlargement of cardiac dullness.

Discharged from hospital after stay of 13 weeks 4 days.

This patient is of interest from the fact that while the state of the pulse and heart gave cause for a certain amount of apprehension, attacks of vomiting occurred. This, as has already been stated, is an ominous sign in a case of diphtheria. In addition to being an indication of impending circulatory failure, the act of vomiting is a severe strain upon an already weakened heart and depressed circulation. In this case, however, the physical signs/

signs did not become more pronounced, as would occur after cardiac vomiting. It was ascertained that the vomiting resulted from an indiscretion in diet, the patient having taken solid food to a greater amount than her condition rendered advisable.

The actual cause of cardio vascular failure in diphtheria is not very clear.

Gee[14] states that the primary debility of the heart is due to the action of the toxin on the heart itself, and that heart failure arises from an interstitial myocarditis with granular and hyaline degeneration of the muscle fibres.

Hibbard[15] found that in fatal cases of diphtheria there was degeneration of the vagi nerves. Hence, it may be thought that the older term "cardiac paralysis" was a suitable term to employ, and it is surely reasonable to suppose that in view of the various paralytic phenomena which may arise in diphtheria as a result of a diphtheritic neuritis, the vagi may also be affected.

It is a very constant sign that shortly before death in a fatal case of diphtheria the pulse rate becomes extremely rapid; in one case I have found it to be as much as 192 per minute.

Various/

Various changes in the heart beat may be observed: premature beats, extra systoles, partial or complete heart block, and systolic bruits.

According to Savill[16], premature beats and extra systoles may be the result of myocardial impairment.

Heart block occurs when there is interference with the passage of the contractile impulse from auricle to ventricle as a result of changes in the Bundle of His, which, as Savill states, may be caused by infective or degenerative processes, diphtheria among the former.

Dilatation of the heart, especially in conjunction with a systolic apical murmur might lead one to suspect the presence of endocarditis, but according to Gee, if such ever occurs, it is probably due to streptococcal infection.

E.B. Gunson[17] divides the types of circulatory insufficiency of diphtheria into

(a) Vascular type

(b) Cardiac type

In the vascular type, death usually occurs in ten days. There is marked prostration, with feeble or almost imperceptible pulse, pallor of the face and/

and coldness of the extremities. The heart acts strongly until within a short time of death. Consciousness is retained throughout. Various haemorrhages - subcutaneous, gastric - may occur. In this condition the peripheral circulation fails, leading to an engorgement of the venous system, resulting in embarrassment of the heart's action.

The cardiac type is regarded by Gunson as an example of cardiac paralysis. Marked arrhythmia, increase in cardiac and liver dulness, and triple rhythm on auscultation are the main symptoms, the pulse remaining good until some time after the onset of arrhythmia.

Observations of my series of cases leads to the opinion that the vascular type of failure is the most common. All the fatal cases except one died before the fifteenth day of illness. It is common to find that there is some degree of cardiac dilatation as shewn by the increased area of cardiac dulness, when an enfeebled pulse draws attention to impending danger from circulatory failure.

Hence, although in agreement with Gunson as regards the theory of a failure of peripheral circulation, I consider that there is also, in these/

these cases, some weakness of the heart muscle contributing to that failure. A vicious circle arises as a result; the venous congestion arising from the failure of the peripheral circulation still further embarrasses the heart, whose musculature is weakened by the action of the diphtheria toxin.

In connection with the above may be considered the opinion of Sergent[18], that in diphtheria there is suprarenal insufficiency. The diminution of the internal secretion of the suprarenals owing to the action of the diphtheria toxin on these organs provides a suitable explanation of the symptoms of failure of the cardio vascular system.

M. Esther Harding[19] considers that the cause of circulatory failure in diphtheria is oligaemia - a decrease in the volume of blood in active circulation - and cardiac weakness. If one accepts the theory of suprarenal insufficiency this would account for the stagnation of the blood in the capillary circulation which she has found.

To sum up: the cardio vascular phenomena in diphtheria cannot be definitely attributed to any one/

one specific condition. They must be regarded as a combination of the afore-mentioned conditions, which, by their united efforts, produce in diphtheria the main source of danger of that disease.

PROGNOSIS.

Attention has already been drawn to the importance of cardio vascular failure in diphtheria as a cause of death, as distinct from involvement of the respiratory system.

In the series of 43 cases in which there was evidence of cardio vascular trouble, death occurred in 28. This, however, scarcely conveys a true impression of the seriousness of the condition. In cases presenting the cardinal signs of vomiting, pallor, feeble pulse, and praecordial pain, the outlook is usually hopeless; of the cases in which these signs were present, only one recovered. The condition of circulatory failure, once manifested by these signs, gradually increases, and it is uncommon for the patient to live longer than two or three days.

There/

There are other conditions which may afford an indication of the prognosis of any case of diphtheria.

The situation and extent of the disease have some influence upon subsequent results. In laryngeal diphtheria, the chief danger at first is of asphyxia from obstruction of the air passages by membrane; then comes the prospect of broncho pneumonia, especially in cases in which tracheotomy or intubation has been necessary. If, however, a laryngeal case can be brought under treatment early, the administration of antitoxin in adequate doses rapidly clears up the danger of respiratory obstruction or extension of membrane down the trachea, with its resultant broncho pneumonia. In laryngeal diphtheria it is uncommon to have death occurring from cardio vascular failure, and with this may be coupled the observation that paralysis are also uncommon. Once the patient has got past the initial danger of respiratory obstruction, he usually makes a good recovery.

In Faucial diphtheria, on the other hand, it is never safe to predict what will be the ultimate result of the disease. Serious or even fatal cardio/

cardio vascular failure may occur in what have been regarded as fairly mild cases. Obviously the danger increases in proportion to the severity of the lesion.

Nasal diphtheria may be regarded as particularly dangerous. During my six months as resident Medical Officer at Edinburgh City Hospital, there were 62 cases of nasal diphtheria; either alone or in addition to faucial, and 15 fatal cases had nasal diphtheria in addition to faucial diphtheria. The danger, therefore, may be said to exist from the fact that nasal diphtheria in conjunction with faucial, implies a severe type of the disease. I have not observed a death from pure nasal diphtheria, but then pure nasal diphtheria is rarely met with in comparison to the amount of faucial diphtheria. The existence of nasal diphtheria usually means that the condition has arisen by extension of diphtheritic membrane from the tonsils and pharynx to the naso pharynx, the result either of delay in obtaining medical attention for the patient, or of failure to recognise the presence of diphtheria and consequently delay in the administration of antitoxin.

antitoxin.

The proportionate danger of diphtheria when a nasal infection is present is well demonstrated by the following figures in connection with the above mentioned period of six months.

Cases of actual diphtheria	554
Laryngeal infection, either alone or mixed	41
Cases of nasal diphtheria either alone or mixed	62
Deaths	33
Number of fatal cases in whom nasal diphtheria was present	15

There are certain symptoms and signs which, when present, enable one to form some opinion as to prognosis.

Cases, usually presenting local lesions of an extensive character, may suffer from haemorrhages. Nose, mouth, and bowel bleed to a greater or less extent; more usually it is in the nature of an oozing of blood; nasal discharge is blood-stained; the stools are streaked with blood; the patient may vomit/

vomit blood, either bright in colour or marked "coffee grounds" material.

In such cases one may also find that there is considerable bruising of the tissues at the site of injection of antitoxin or other drugs. There may even be petechial haemorrhages or purpuric spots, the neck and chest being favourite sites.

These haemorrhagic cases form the most grave type of diphtheria and are invariably fatal.

Albuminuria is present in a considerable number of cases of diphtheria, but it is a sign indicative of a fairly acute attack. In conjunction with any of the signs of cardiac vascular failure it is to be held as tending to an unfavourable prognosis. Haematuria is rare in diphtheria; should it exist it is most likely to be evidence of the case being an example of haemorrhagic diphtheria, rather than an acute nephritis.

As regards the cardio vascular system, the broad statement may be made that as long as there is any sign whatever of weakness, the prognosis must be guarded. The presence of enlargement of the area of cardiac dullness necessitates a careful watch/

watch being kept for any sign of failure of that system.

If the pulse rate becomes very rapid, or if there is a sudden change in its rate, the patient is in danger. If the pulse rate rises above 140 to 160 per minute, the prognosis is usually hopeless.

As regards a slow pulse rate, this should be regarded with some anxiety, as it may be a sign of impending heart block. One patient of my series, a boy, aged 6 years, had a pulse rate of 48 to 54 per minute for a fortnight. In addition, the pulse was feeble. The apex beat was in the 6th interspace ½ inch outside the nipple line; right border of heart 1½ inches from mid sternal lines; a systolic bruit at apex, with diffuse pulsation over praecordial area; a tendency to cyanosis of cheeks and lips. The boy ultimately made a good recovery.

The appearance of gallop rhythm is a sign that the patient's condition is hopeless, and death almost invariably occurs in twelve to twenty-four hours. When this stage has been reached, there is usually to be found some enlargement of the liver dullness; the lower border may even be palpable.

This/

This, too, is a sign of the appreach of death.

Severe arrhythmia is by no means infrequent in diphtheria, but according to Mackenzie[20]; it is of no great prognostic importance.

The question of the duration of the disease at the time when it is first brought under treatment is of importance. Obviously a case which is seen on the second day and is promptly and effectively treated with an appropriate dose of antitoxin has a much more favourable prognosis than one which is not recognised until the seventh day. By that time the diphtheritic membrane may have become very extensive in distribution, and there is a corresponding toxaemia. Sufficient toxin will have been absorbed to cause serious or even fatal cardio vascular trouble. Moreover the administration of antitoxin is not nearly so effective at such a late period in the disease, the toxin is fixed in the tissues and neutralised only with difficulty by the antitoxin.

The question of age of the patient has a certain bearing upon prognosis. All my cases have been children; adults seldom contract serious cardio vascular/

vascular trouble in diphtheria, but it must be remembered that diphtheria is essentially a disease of children.

TREATMENT.

The treatment of the cardio vascular trouble of diphtheria is to a considerable extent dependent upon the efficient and early treatment of the primary lesion. That is to say, a case of diphtheria which receives early recognition, and is given antitoxin in adequate amount is unlikely to receive attention owing to symptoms of cardio vascular failure.

In giving antitoxin, due regard is made to the situation and extent of the lesion and to the duration of the disease. At the Edinburgh City Hospital, a dose of 3000 units is given to a case presenting diphtheritic membrane on the tonsils and in the second day of illness, another thousand units being added to the dose if the case is in its third day. If there is membrane on the soft palate or uvula or posterior pharyngeal/

pharyngeal wall, 6000 to 8000 units would be given. A severe case with extensive distribution of membrane and an obviously toxic appearance would be given 8000 or even 10000 units on admission, and a second or even further doses of 8000 units at the end of eight to twelve hours, should the local lesion shew no signs of clearing up. Doses of 30000 units or more will be required in cases which have not come under treatment until the fifth to seventh day, and present signs of marked toxaemia with very frequently a naso pharyngeal infection in addition to the faucial lesion. Laryngeal cases are given 6000 to 8000 units, repeated at intervals of eight hours up to a total of 24000 to 32000 units.

Local treatment consists in the application of mild antiseptics to the throat, e.g. boroglyceride, or if the patient is able, gargles of dilute listerine or eusol. The application of strong antiseptics to a diphtheritic throat is undesirable.

The above may be considered as the specific treatment of diphtheria; but to ward off any possible cardio vascular symptoms the most essential thing is rest in bed in a recumbent posture/

posture until such danger may be considered to be past. In a mild example of diphtheria - 3000 units - the patient is kept in bed with only one small pillow until the end of the second week. He is not allowed to sit up in bed on any pretext. During the third week he may be gradually raised, and at the end of that week, provided that the condition of the cardio vascular system is satisfactory, he is allowed up for a short time, being discharged at the end of four weeks if examination of throat swabs reveals absence of diphtheria bacilli.

Severe cases of diphtheria, - 8000 units or more - are kept recumbent for at least six weeks, then gradually raised in bed, and are not allowed out of bed unless the state of the heart and pulse is satisfactory. These measures largely prevent a sudden cardic vascular failure proving fatal to the patient, a tragedy which should not occur if the patient is kept at rest for a sufficient period.

If any of the signs of cardio vascular failure appear - vomiting, syncope, praecordial pain, and weak pulse - the foot of the bed is elevated on blocks, and appropriate measures are taken to deal with/

with this. It is advisable to cut off all food by the mouth, and administer nourishment in the form of nutrient enemata and saline solution per rectum.

It is a routine procedure at the City Hospital to give all diphtheria patients stimulants in the form of Liquor Strychninae, mT or mTT. and Whisky, 3p to 3i according to age, every four hours. This may to some extent prevent the onset of circulatory depression.

When cardiac paralysis has actually manifested itself, the only drug treatment likely to be of any avail is by the intramuscular injection of Adrenalin, and of Camphor in Olive Oil (sterilised).
The former is recommended by Rolleston[21], and in view of the theory previously advanced that there is a suprarenal insufficiency in diphtheria, it may be expected to do some good.

Adrenalin raises the blood pressure and also acts as a stimulant of the heart. Its effect is not persistent however. In all severe and toxic cases of diphtheria the administration of adrenalin should/

should be started early in the hope of averting any tendency to circulatory failure. Doses of five to seven minims intramuscularly every four hours are given.

The effect of camphor as a cardiac and circulatory stimulant is more prolonged than adrenalin; it is given intramuscularly in doses of one to three grains dissolved in sterile olive oil every four hours, or alternately with injections of adrenalin.

The application of hot fomentations over the heart may be employed with the object of causing a reflex stimulation of that organ.

The question of dealing with the profound restlessness and mental anxiety present in many cases of diphtheritic circulatory failure should receive attention. I have found in some of my cases that a dose of Morphia and Atropin hypodermically in amount appropriate to the age of the patient has been of considerable advantage. There can be little doubt that in a restless patient the heart and circulation are being subjected to a strain which they are in an unfit state to endure.

Hence,/

Hence, any measures which may diminish that strain are useful, and a few hours of sleep, or even merely rest, secured by an injection of Morphia and Atrophin will give rest to the weakened heart.

It must be confessed, however, that in the cardio vascular failure of diphtheria, treatment is most disappointing. It may prolong the life of the patient by a day or two, but in almost all cases which have presented the cardinal signs a fatal termination occurs in spite of all treatment.

If some specific treatment could be found for the cardio vascular complications of diphtheria as effective as the antitoxin is for the initial local lesion, the mortality from the disease would be to a great extent abolished. Doubtless, in time some means will be found, but at the present day the cardio vascular complications of diphtheria constitute by far its gravest danger.

CONCLUSIONS.

I. Cardio vascular failure is the cause of about 75 per cent of the deaths from diphtheria.

2. The prospect of its occurrence varies almost directly as the duration of the disease when first brought under treatment.

3. The severity of the attack of diphtheria has a considerable influence upon the incidence of cardio vascular complications, which, however, may supervene in mild cases.

4. Suprarenal inefficiency combined with actual cardiac weakness affords the most reasonable explanation of the cardio vascular complications of diphtheria.

5. Treatment is usually ineffective in cases presenting all the cardinal signs.

I am indebted to my former chief, Dr Claude B. Ker, for his courtesy in affording me every facility for this work.

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