Thesis for the
M. D.

University of Edinburgh.

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Briton Ferry

In the following Thesis I propose to record a few clinical observations and impressions gained from the study of cases of diptheria in my own 26 years practise in Briton-ferry. My object is to record clinical phenomena observable in a series of epidemics occurring in Britonferry in the last 26 years.

HISTORY. There is no evidence that the Greek physicians had any knowledge of the disease, but it was well known in Egypt, Syria, and Palestine in ancient times, this is proved by the frequent references to it in the Babylonian Talmud, and its eastern origin is more than probable as indicated in other writings and even paralysis of the palate was referred to in the sixth century. Throat pestilences and plagues were mentioned by ancient writers, as causing great mortality among children, for example in the year 1004 in Rome--in certain provinces of the Byzantine kingdom in the year 1039. An epidemic of feverish angina occurred in Germany along the Rhine in the year 1628. A very severe epidemic of the disease occurred throughout the whole of Spain and Italy in the sixteenth century--and in this epidemic accurate descriptions of the false membrane were given, and an Italian physician pointed out that the disease usually began on the tonsils, uhula or throat, but may also arise in the larynx or sometimes in the nose, even the horrible smell from the mouth was mentioned. 
In 1748 Rothergill referred to it in this Country as sore throat with ulcers. The disease was already epidemic in New York in 1771-2. In 1765 Francis Home of Edinburgh published a small work on the nature of croup, this was the term given to diptheria when the larynx was attacked, and his account of the post mortem findings were very accurate - Holmes noticed how the disease occurred among children and he considered cold damp weather in the winter months as a predisposing factor. It seems that Home's publication aroused the attention of the whole Medical world. A little later Samuel Bard of New York wrote a very elaborate account of suffocative angina, and diptheria is at once recognised in his description of this disease. The virulent outbreaks of the disease in France in 1821 gave Bretonneau the material for his investigations and it was during this epidemic, he gave the name "diptherite" to the disease, and the production of membrane was to him the characteristic mark of the disease. Bretonneau very clearly distinguished between the Scarlet fever and the diptheria angina, in the latter he said the membrane was formed on the mucous membrane whilst in the former the change was in the mucous membrane itself. Epidemics of the disease were recorded throughout the whole world and it is said that in 1866 a very severe epidemic occurred in China from which 25,000 people are said to have died. In 1855 Bretonneau
asserted his conviction that all forms of the disease were contagious but his attempts to produce the lesions of diptheria in animals by the inoculation of material derived from patients met with no success. Professor Laycock of Edinburgh declared that diptheria was due to the development of _staphylococcus albiuons_ and there is no doubt that false membranes were produced by the inoculation of some of these fungi by many experimenters. But in 1881 Klebs found the specific Microorganisms in large numbers in the membrane, and he even obtained a growth by cultivation experiments on thin layers of gelatin, but it was Loeffler who fulfilled the three postulates of Koch with regard to the relation of micro-organisms to a disease, he isolated and obtained a pure culture of the organism and experimentally reproduced the disease with the pure cultures. In the treatment of diptheria Loeffler advised the isolation of the individuals affected and to destroy all materials and secretions. In 1888 Loeffler came to the conclusion that the bacilli produced a poison which acted injuriously on the organs of the animal inoculated, and he was successful in obtaining a weak poison by extraction with Glycerine but Rouseyrsin worked with older cultures and obtained a much more powerful poison. The next step was the differentiation of diptheria bacilli from pseudo-diptheria bacilli and this required a long investigation but in 1897 Neisser discovered a special method of staining diptheria bacilli
and the granule staining has on the whole stood the test of extensive subsequent use. The presence of diptheria bacilli in the throats of healthy individuals prevented the acceptance of the diptheria bacillus as the causal factor. The specific antitoxin was elaborated by Behring and the modern treatment dates from the discovery of this antitoxin. The next step was the standardising of the serum by Ehrlich and Behring and in 1893 the making of the serum on a commercial scale was commenced and in the following year its employment was general over Europe & America. The Antitoxin used in the treatment of diptheria in the human subject is the blood serum of Horses that have been immunised by repeated injections of diptheriatoxin.

Epidemiology of Diptheria.

The relationship between dry years and diptheria has been exhaustively analysed by Dr Longstaff and he found the correspondence close in the sixties and early seventies but least marked in later years, and Sir A Newsholme has concluded that the essential factor in the production of diptheria, is the occurrence of a succession of years of deficient rainfall associated as they are with abnormally dry conditions of the subsoil, but in my experience in Britonferry epidemics of diptheria occur in wet periods, and in my opinion the continuous dampness of the soil appears to favour the persistent prevalence of
diptheria in Britonferry. In the month of September 1918 I had three cases of Diptheria and this month had a very heavy rainfall - the record was over 8 inches of rain - also I had two cases in December 1918 and this also was a particularly wet month in West Wales. In the year 1916-17 I saw nine cases of diptheria and this also was almost a record winter for rain. There is no doubt the disease shows an Autumnal prevalence and there is evidence to show that the mortality is highest in the months of September, October, November & December - and as a rule these months have the heaviest rainfall for the year, and in my experience the prevalence of diptheria is increased when there is slush in the streets. Britonferry is flat and lies on a level with the sea, and the physical conditions are such that they favour the retention of moisture in the soil, it is also exposed to the influence of cold wet winds and sore throats and bronchial cataarrh are very common ailments in the place.

Modes of infection.

The disease is very contagious and infection from one person to another is the most important factor in the spread of diptheria, then infected articles such as spoons and drinking vessels may convey the bacilli - cases have been traced to nasal cataarrh and I had a very good instance of the latter in my own practice in February 1918. I was called to a case of typical faucial diptheria and after the
usual treatment the child got quite well—but I was curious to know the origin of this case and when called to a house next door but one in the same street, I noticed a child with a thick nasal discharge. I was at once suspicious and took a swab and sent it away for examination and my suspicions were confirmed by the report—the child was isolated and treated, otherwise I am convinced that the child would have been the cause of a sharp epidemic in the neighborhood.

I have seen no cases of diphtheria due to infection of milk but this has been proved to be quite possible, and in my experience defects of drainage have not been factors in the causation of diphtheria. The increase of diphtheria of late years is no doubt due to the density of population and the aggregation of children in board schools—the effect of the aggregation was clearly proved in the Medical report of the Canadian contingent in this War—whilst the soldiers lived in tents, epidemic throat diseases were not prevalent, but when they were removed into huts diphtheria and other throat affections became quite common. In one epidemic I had in this place among infants I had reason to destroy the school books that had been in use—with the result that the epidemic ceased in a very short time.

AGE. It is essentially a children's disease and in my experience it is rare among adults.
The majority of my patients have been over 5 years of age but under six & sex seems to play no part in the disease. - The disease is certainly the more fatal the younger the patient. One case of the disease has been recorded in a child nine days old, but personally I have not seen a case under 12 months old.

FAUCIAL DIPHTHERIA. It is unnecessary to describe this or the forms it assumes, but in a busy practice how it is to miss Diptheria unless the throat is examined, for it is a common place observation that Membrane extensive enough to cover a large part of the tonsil may exist with only the very slightest malaise, indeed in some cases the patient may be unaware that the throat is the seat of the mischief. The local lesions are due to the action of the toxins secreted by the bacilli, and generally begins in the tonsils or the larynx - it was confined to the tonsils alone in twenty of my cases. - The infection rarely begins in the conjunctiva - It may spread from the larynx to the trachea and lungs - from the nose to the accessory sinuses and to the middle ear - the membrane is really an adherent layer of fibrin, and the bacilli occur in clumps of various sizes on the surface of the membrane and also in the underlying necrotic tissue, they are not found in living tissue. The membrane varies greatly in appearance - I have seen it white - dirty white - brownish or almost black in colour. But it is often difficult to distinguish between certain throat affections, and true
Diptheria thus in Tonsilitis, due to Streptococci and Staphylococci, phimococci. You may have a suspicious looking membrane in Vincent's Augina, or that due to Hofmans Bacillus. I have seen a membrane in Thrush, and you may have it in Scurvy. In Scarlet Fever you always have a faucal inflammation which is suspicious, and it may also be present in Measles, Typhoid and Typhus Fever. I have never seen a Diptheroid Inflammation in Whooping Cough and I have seen hundreds of cases of the latter. In all my cases of Diptheria I have never seen sloughing of the mucous membrane - but occasionally I have seen a few superficial ulcers, and it must be remembered that these cases of Diptheroid Inflammation occur in children, and generally in the Autumn and early Spring.

and they can only be differentiated from true Diptheria by bacteriological examination.

Temperature in Diptheria. This is generally raised from the beginning - in some of my cases it has reached 104, but this temperature does not last long - In four of my cases there was no rise of temperature.

Nasal Diptheria. This is often unrecognised and discharges from the nose should be more frequently examined.

Laryngeal Diptheria. This is generally associated with Faucial Diptheria, but I have certainly seen it occur independantly of the faucial attack, and then dyspuoca or obstructed breathing is the first symptom with a harsh
metallic cough. But as a rule it is secondary to Faucial diptheria, and in my cases the invasion of the larynx took place in the first week. - In my practice I have not seen a single case of laryngeal diptheria since the introduction of antitoxin - but I am convinced that in many of my cases - extension to the larynx would have taken place if antitoxin had not been given a second and a third time I had to perform tracheotomy six times in the first three years of my practice in Briton Ferry, i.e., in the pre-antitoxin days but not once since then. In progressive laryngeal diptheria you get marked inspiratory stridor, cyanosis and recession of the ribs during inspiration, the voice is reduced to a whisper - the lips and fingers tips become blue, and in some of my cases protrusion of of the eyes was marked. - In my cases the temperature was not high, but the pulse rate was always increased. Bronchial Pneumonia may complicate laryngeal diptheria, but in my experience lobar pneumonia is rare. I strongly advocate the use of steam in tracheotomy cases for deaths may be due to obstruction of the trachea by inspised discharge.

Albuminuria is frequent in diptheria - it was present in just over half of my cases, and I generally found it on the third day of the disease, and as a rule it disappears in about ten days. - I believe nephritis is rare in diptheria, in any case I have never found any epithelial casts on microscopical examination of the urine, and the lessened output of urine is due in many cases to loss of vascular tone from cardiac weakness. Albuminuria is more
frequent in fatal than in none fatal cases. The vomiting in diptheria has been said to be due to uraemia, but it occurs though rarely when the urine is free from albumin.

Complications.-Paralysis early, and full doses of autitoxin lessen the frequency of Paralysis and its severity when it occurs. - Gower stated that Paralysis was equally to follow attacks that are severe as those that are trifling, and this appears to have been the general opinion, especially before the autitoxin treatment was discovered. In looking up the incidence of paralysis I have taken the report of the Metropolitan Asylums Board Report for 1900. - The classification depends on the amount of the local lesions.

<table>
<thead>
<tr>
<th>Nature of Disease</th>
<th>Total cases</th>
<th>Paralysis Cases</th>
<th>Paralysis Deaths from Severe Par. Paralysis</th>
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<tbody>
<tr>
<td>Severe</td>
<td>223</td>
<td>64</td>
<td>19</td>
</tr>
<tr>
<td>Moderate</td>
<td>566</td>
<td>75</td>
<td>7</td>
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<tr>
<td>Mild</td>
<td>40</td>
<td>4</td>
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From the above table the following conclusions may be drawn:

(1) Severe attacks of Diptheria are especially liable to be followed by Paralysis, often of a severe character.

(2) In less severe attacks Paralysis is less frequent.

In my experience indications of the severity of diptheria are found in the urine, the blood, and the heart.-

Albuminuria, anaemia and disturbance of the hearts action are most marked in the severe cases, and each one of these signs serves as a warning of the possible approach of Paralysis. But in the treatment by Autitoxin mild cases are prevented from becoming severe. The Paralytic symptoms were at one time supposed to be due to uraemia, and of
course the considerable frequency of albuminuria in diptheria is universally admitted, but paralysis may occur without the presence of albumen in the urine. Gee held that Paralysis was very rare after laryngeal diptheria, no doubt because the patient died before it had time to develop, but there is no doubt that the serum treatment by increasing the number of recoveries from laryngeal diptheria has also increased the number of cases which are likely to develop paralysis.
The nervous sequence of diphtheria are paralysis of the palate with its symptoms. The affection of accommodation and polyneuritis. The diphtheria toxin is said to have a selective action on cranial nerves and their nuclei. Paralysis has been produced in animals by the injection of diphtheria antitoxin but cranial nerve involvement is not so characteristic in animals as in man. If the diphtheria is extrafacial the palate is not paralysed, and there is no doubt there is a distinct relationship between the paralysis and the site of the infection, thus paralysis of the palate is an ascending neuritis comparable with that occurring in tetanus, but the ocular and polyneuritic symptoms cannot be accounted for thus, but must be due to the toxin circulating in the blood, and thus reaching the whole nervous system (ref. Orr Rows Brain 1913-1914. 271). On the other hand several observers have recorded polyneuritis after wound diphtheria. Respiratory paralysis is very fatal, yet even very severe cases have been known to recover. I have never seen a case of relapse in diphtheritic paralysis, but this has occurred—it is probably due to some liberation of toxin stored up in some place in the body. The danger of food passing into the air passages is a real one in diphtheritic palsy, and death has resulted from this. Osler and others maintain that paralysis follows relatively more often upon the diphtheria of the adult
than of the child, but Poord Cadger says that young children are more frequently affected than older ones. The changes in sensation are usually slight in Diptheritic Paralysis, and difficult to prove in children - but I have certainly noticed loss of sensation in the palate, and this has enabled some observers to foretell the visit of paralysis some days before it appears. Recovery from the paralysis will occur if life is preserved, and in general the prognosis is good except in the cardio-pulmonary forms. In the cardio-pulmonary form death may occur by paralysis of the heart or respiration, but of course this cardiac failure may be due to an intense and acute degenerative myocarditis, and not the result of an affection of the cardiac nerves.

Prognosis. Early appearance of the paralysis is of evil import and if the paralysis is accompanied by severe albuminuria the case is more serious since this would show a more profound intoxication.

Treatment. If the paralysis is a toxin manifestation then any treatment which antagonises this intoxication should on theoretical consideration at least lessen the liability to paralysis, and there is no doubt that if liberal doses of antitoxin are given early in the illness, the subsequent paralysis is favourably influenced, and this beneficial influence is likely to manifest itself on such symptoms as failure of the heart, but severe cases of diptheria are likely to be followed by some paralysis in spite
of even large doses of antitoxin. Rest is of great importance in the preventing and the treatment of paralysis. I had a severe case of diptheria followed by paralysis in December 1918 - and I took full notes of the case. I was called to see a girl 10 years of age on December 21st, 1918, suffering from a sore throat - temperature was 104 - pulse rate 140, and a respiratory rate of 34. - There was no doubt she was suffering from diptheria, and a swab taken from the throat proved positive. - Serum was injected subcutaneously. - The patient looked pale and toxic, but was well nourished. The tongue was thickly furred - breath offensive - the throat was much injected, and the tonsils were completely covered with a false membrane, as was also most of the soft palate - there was bilateral cervical adenitis, more marked on the right side. - Heart sounds were quick and soft in character, and the pulse rapid and compressible.

December 22nd, Throat condition practically unchanged - but pallor of the face was extreme. - Serum was again injected, and also an Alkalin. Moisture was given for acidosis has been shown to occur in diptheria.

December 26th. A slight stridor on inspiration was noticed, and another injection of serum was given.

December 27. Exhaustion was marked and the child was very ill - the heart was irregular and blood pressure low. Brandy was ordered.
December 30. There was evidence of paralysis of the palate, nasal speech was pronounced. Soft palate immobile, and sensation lost. There was also slight difficulty in deglutition, urine - albumen present. January 4th. The palate was still immobile, but on January 8th speech was becoming more normal, and on January 10th the palate became freely mobile, and sensation returned. The palatal palsy was bilateral. The persistence of the paralysis in this case in my opinion depended on the serious and complete faucial involvement, and the condition presented a toxic neuritis of the Glosso-pharyngeal nerve. (see Thesis for other cases recorded.)

Heart Failure. Death is often due to cardiac failure and may take place quite suddenly, and thus it is very important to notice the state of the pulse. The occurrence of syncope - vomiting and a frequent or irregular pulse are exceedingly unfavourable symptoms. Heart failure occurs in two forms.
1. Slow progressive cardiac weakness from the commencement of the illness - the case presents the appearance of profound exhaustion - the pulse is regular but soon becomes weak and frequently disappears entirely from the wrist, and there is a rapid lowering of blood pressure, the extremities become cold and clammy and in the later stages cyanosed. There is little or no increase of cardiac dulness and liver dulness is generally normal; death is often preceded by a convulsion. I had an example of this form of cardiac failure in my practice last March (1917). I was called to a boy aged nine years suffering from a sore throat. On examination I found he had severe faucial diptheria with considerable swelling of the glands of the neck. Subcutaneous hemorrhages were present in the lower limbs and the latter were cold and clammy. The pulse was weak but regular and on percussion there was no evidence of increased cardiac dulness. The temperature was 99.1° and at night the patient was very restless. On the fourth day the pulse was 125 per minute and extremely feeble and the temperature was falling; he died suddenly on the morning of the fifth day. 8000 units of antitoxin had been administered subcutaneously.

2. There is another type of cardiac failure observed in diptheria and in these cases it is always necessary to be on the look-out for any alteration in the pulse such as infrequency, acceleration and irregularity, for the cardiac failure is generally preceded by a severe
arrhythmia and you may have paroxysms of regular tachycardia. The onset of arrhythmia usually occurs about the third week. The cessation of the arrhythmia and the return to slower pulse rate is quickly followed by the disappearance of the signs of the circulatory failure. The drug treatment of this condition is most unsatisfactory. Digitalis, strychnine, and a solution of adrenalin having been injected subcutaneously without any success.

Warmth and brandy may be of some service but most important of all is the enforcement of complete rest. Vomiting occasionally occurs in iptheria and when associated with cardiac failure and a scanty albuminous urine, is a grave prognostic symptom.

In these cases no food should be given by the mouth, but sips of water may be given for the thirst and rectal feeding should be attempted.

Records of cases of Paralytic in my practice

I, Davies. 83 Hunter St. Here, two children, a brother and sister, were attacked by sore throat. Iptheria was diagnosed and the usual treatment followed with the result that the throats were cleared of all exudation and membrane, but in ten days both complained of difficulty in swallowing, and fluids returning through the nose. The character of the voice in both cases altered and on examination of the throat, the palate was found to be motionless. They both remained in this condition for two months, but after that gradual recovery took place.
Rees. Rockingham Terrace. This boy, aged 8, was attacked with severe diphtheria but eventually recovered, but when he went to school he complained of defective vision. On examination, I found paralysis of accommodation; distant vision was good but near vision was defective. This case also ended in complete recovery.

3. I attended a boy of six years of age for diphtheria. He was injected, and apparently, there was complete recovery, but in four weeks he developed unsteadiness in gait. He walked with his legs wide apart and he swayed when the eyes were closed, and the feet placed together, no knee reflexes could be obtained. The boy steadily improved and in a few months knee jerks had returned. The treatment of diphtheria paralysis consists of rest in bed and massage of the muscles — with strychnine internally.

Adjuncts to Serum treatment.

These consist of general, local and operative treatment, and as regards the latter, as mentioned before I have had no occasion to perform tracheotomy since the introduction of antitoxin treatment — and some of the cases on whom I had to perform tracheotomy are living in Briton Ferry at present. Intubation has been recommended by some authorities instead of tracheotomy but I have had no experience of this, but I saw it performed once by the late Professor Mandale of Edinburgh.
Haemorrhage and changes in the blood.

These symptoms usually indicate a very malignant type of the disease, and the haemorrhage may be subcutaneous, submucous, or subserous. The condition is due to the toxaemia, and they testify to the severity of the blood infection, and the involvement of the capillaries.

Diptheria Bacillus. There is no doubt there are various strains of the Diptheria Bacillus, but these are identical in cultural reactions, and pathogenic properties. There are other bacilli resembling the diptheria bacillus which are frequently found in the throat, nose, skin, and general organs. These are known as Pseudo-diptheria bacilli. Some restrict this term to the nonvirulant forms of the diptheria bacillus, others restrict the term to the organism called Hofman's Bacillus. The latter is present in the normal mouth and nose. The xerosis bacillus is a diptheria like organism found in the eye.

The diptheria bacillus has been found in the throats of healthy persons. The bacillus is a non-mobile rod shaped microorganism with often a beaded appearance, and the rod ends are usually rounded. Neisser's method of staining the bacillus is very reliable, and it clearly brings out the characteristic polar bodies of the bacillus. But I usually employ the dilute methylene blue method in my practice, but the staining is inferior to that obtained by Neissers.
method. - The bacillus possesses considerable powers of resistance especially if kept in the dark at room temperature, but it is characteristic of the bacillus that it varies in virulence, but most writers agree that the degree of virulence has no relation to the severity or mildness of the disease in the patient. - This depends more on toxin production. Hofman's Bacillus bears no causal relation to the disease, but it is sometimes associated with the diptheria, but it is also a common inhabitant of the healthy mouth, and nose, especially of children. Attempts have been made to convert Hofman's Bacillus into the diptheria bacillus and vice versa - but these experiments so far as they go point to the non-identity of the two organisms, and Hofman's Bacillus shows no virulence to guinea pigs to man. - Diptheria Bacilli found in the throats of healthy contacts are fully virulent and retain their virulence for long periods. When streptococci are present with the diptheria bacillus you may have secondary suppuration of the lymphatic glands, and they also take a large part in the causation of lobular pneumonia which so frequently complicates diptheria, and it has also been stated that the presence of streptococci in the throat increases the virulence of the diptheria bacillus.
Prophylaxis and treatment. This section may be divided into three parts.

1. Measures to be adopted for the prevention and control of the disease.
3. Adjuncts to Serum treatment.

(1) Diphtheria is easily communicated from person to person and immediate isolation of the infected patient should be attempted. An isolation hospital is the best means of attaining this, but if the patient has to be treated at home, he should have a room exclusively reserved for himself and all expectoration and discharges from the nose and other affected parts should be destroyed by burning and at the termination of the illness the room and contents should be thoroughly disinfected; but long after the disappearance of false membranes the bacillus is present in the secretions of the throat and nose, and in apparently normal individuals the Bacillus Diptheriae may be harboured in the depths of the tonsillar crypts, and some authorities have proved that complete enucleation of the tonsils is a successful means for eliminating diphtheria organisms from carriers, and I believe this has been done during the present war in several outbreaks of diphtheria.

Mild cases of diphtheria are frequently overlooked and this is often the cause of a recrudescence of the disease after the re-opening of a school; and one of the principal factors in the persistent prevalence
of Liptheria is not the carrier but these mild unrecognised cases. In the case of the carrier the bacilli are probably non-virulent and have no causal relationship to cases of Liptheria.

**Serum Treatment.**

This is either prophylactic or curative. The manufacture of Liptheria antitoxin has reached a high standard of excellence. The Serum may be given in several different forms viz. ordinary grade, concentrated serum, antitoxin globulins, or dry serums. The dosage is calculated in Ehrlich's system of units and antitoxin is taken as a standard, and a large quantity is kept and is from time to time supplied to manufacturers who use it for standardising their own toxin. By this means they are able to test the antitoxic value of the Sera which they themselves manufacture. With the increased knowledge of the best methods of immunisation of horses, the antitoxic value of the Sera has risen considerably in recent years, but the higher strengths (500 units to 1,000) are difficult to prepare, but the diminution of the quantity of serum to be injected is a very important advantage, as a large number of units can be injected in a small bulk of serum and so minimise the risk of the appearance of Serum Sanguisae.

**Antibacterial Liptheria Serum.**

The ordinary antitoxin does not affect the bacteria themselves and thus an attempt has been made to prepare an antibacterial Serum. Instead of injecting the Serum
an extract of the dead bacilli is made and injected into horses. This fluid gives rise to the formation of an agglutinin in the Serum which acts upon the bacilli. The exact nature of the bodies in the anti-bacterial serum is still a matter of doubt. They are considered to be of the nature of opsonins which act upon the diphtheria bacilli and render them a more easy prey to the phagocytes.

The advisability or otherwise of employing Diphtheria Antitoxin as a prophylactic has been much discussed of late, but the immunity conferred is only of a temporary character, and Goodall on account of the fear of anaphylactic shock, considers the indiscriminate use of antitoxin not only unjustifiable but also unnecessary. Emery in his book on specific therapy and immunity recommends a prophylactic dose of 1,000 units. The serum for this purpose may be given by injection or by the mouth, but before using the serum, an enquiry should be made to the previous history of the patient, such as asthma—a previous injection of serum. In virulent epidemics it might be of great service.

The Curative Treatment.

The early administration of antitoxin is most important; it is inadvisable to wait for a bacteriological diagnosis of the case. The majority of statistics showing the results of early and late administration of the Serum are misleading, because the onset is not often attended by any grave symptom. In an industrial practice like mine I am not consulted until the parents have become alarmed after the disease has been in progress for several days. It is however, a well
recognised clinical fact that the earlier the antitoxin is administered the more likely is the patient to recover. In my own practice the fatal cases occur in patients who had been ill for an indefinite period before receiving treatment.

Opinion varies as to dose of antitoxin to be administered; personally, I never give less than 4,000 units, injected subcutaneously, and if the membrane tends to extend and the local exudation is slow to yield, the dose is repeated within 12 hours. The severity of the symptoms and the progress of the case are the only guides to the number of injections and the amount of antitoxin to be used. It is quite safe to give up to 20,000 units, beyond this limit it is rarely necessary to go.

In laryngeal diphtheria I start with 8,000 units and this is repeated twice or thrice at a twelve hour interval according to the degree of obstruction.

Clinical effects of hypodermic administration of antitoxin.

The tumour caused by the injection disappears in less than half an hour; occasionally a certain amount of redness remains for some hours and this area may itch considerably. In rarer conditions a raised dull red condition of the skin may be seen, accompanied by a rise of temperature and some general malaise. The general effects are mainly dependent upon the earliness or otherwise of the institution of the serum treatment. In simple cases there is usually a rise of temperature
within an hour or two, accompanied by a quickening of the pulse rate. If the case is one of pure Diptheria, the temperature generally returns to normal in 48 hours, but if however the infection is a mixed one and coccii are present, then the fall of temperature is considerably delayed - similarly adenitis, broncho-pneumonia may also delay the fall. On rare occasions the patient may be subjected to repeated attacks of sneezing and certainly in some laryngeal cases the dyspnée becomes more pronounced a few hours after injection. Individual peculiarity and susceptibility to certain unknown elements contained in the serum are probably the cause of these symptoms.

**Effect upon the Membrane.**

This is best observed in simple cases of tonsillar diptheria. In about 10 hours the spread of the membrane is stopped and the edges of the patch become detached from the underlying tissue. This separation continues and the membrane may be cast off in its entirety or in pieces. Slight haemorrhage may accompany the detachment. Such rapid effect is only seen in simple cases coming under treatment early. In those in which toxaemia is profound, little or no effect on the general condition is seen, but I have never seen severe hemorrhage from separation of the membrane. If there is no change within 12 hours the question of giving more serum must be considered. The "solvent" effect of the serum is more apparent in the tonsillar lesions than in other pharyngeal situations. If the membrane has not
disappeared by the fourth day after the commencement of serum treatment the prognosis of the case is not at all favourable.

Laryngeal Diptheria. It has been mentioned that in some instances the dyspnœa is rendered temporarily more urgent after injection of the serum. This may be due to a mechanical cause, the throwing into the circulation a comparatively large amount of fluid in the form of ordinary grade serum causing congestion and swelling of the mucous membrane, or it may be one of the phenomena of anaphylaxis. If Tracheotomy has been performed the membrane loosened from the lower respiratory tract commences to be expelled from the tube, either in small shreds or definite casts of the trachea and bronchi. It is seldom necessary to leave the tube in more than three days and in favourable cases it may be removed much sooner. Diptheria sometimes affects the middle ear - conjunctiva or valva and in these cases local treatment usually suffices - nasal diptheria may occur separately or in connection with diptheria of the fauces and in the latter the disease is usually of a virulent type. A weak solution of Sodium Bicarbonate is often useful as a solvent of the thick nasal discharge. The effects upon the constitutional symptoms are likewise impressive. The general condition of the patient improves noticeably within twelve to twentyfour hours - the constitutional symptoms of toxalmia disappear - the color and general appearance are altered and the appetite begins to improve.
Technique of Serum Administration.

Serum may be given subcutaneously, intravenously, by the mouth or per rectum. I have also given it intramuscularly with good and rapid results. I have given it by the mouth the first thing in the morning on an empty stomach, mixed with a little Sodium Bicarbonate, but I have had no confidence in this method and I have only given it in suspicious cases of Diphtheria. Abstention from food for four hours is recommended after giving Serum by the mouth. The oral method may be employed as an augmentation to hypodermic injection and also as a prophylactic in "contacts". It is said that anaphylaxis is rare after oral administration, probably due to the fact that less serum is absorbed by the stomach than after injection, or to the altered condition of the serum from the action of the gastric juice.

Subcutaneous method. This method has been and still is the orthodox means of administration with the general practitioner and he takes great care that the site of injection, the syringe, and everything connected with the operation should be as near aseptic as is possible. I have always been accustomed to inject into the loose tissues between the shoulders, and from clinical experience there is no doubt that some of the serum is absorbed into the circulation in about eight hours. I have never seen any serum abscess as a result of the injection.
The Intravenous Method. I have never tried this method. It is not easily done in children but some observers speak highly of the prompt and beneficial action which they have obtained by this method. It is generally given suspended in normal saline, but when I can I prefer to give the serum intramuscularly because undoubtedly the effect is more rapid as the serum appears in the blood sooner than by hypodermic injection. I inject in the upper and outer quarter of the gluteal region to avoid injuring any blood vessels.

Anaphylaxis and Serum sickness.

In Specific Therapy the aim is to increase the patients fund of Specific antibody and for this purpose, immune serums is one of the practical methods available. This method supplies him with antibody already made by an animal such as the horse in response to vaccination. The best known of the immune sera is that which contains diphtheria antitoxin. Anaphylaxis may be defined as a specific sensitiveness to foreign proteids. In immune serums, the animal chosen is in almost all cases the horse on account of the ease with which serum can be obtained from this animal in large quantities, under sterile conditions, and the relative freedom of horse serum from toxic action on most patients, as compared with that of some other species. But it was found that the injection of serum of non-immunised horses produced the same
phenomena as immune serum. This phenomenon of anaphylaxis is as follows.

If an animal is given a dose of serum of another species - be that dose even a minute one - and an interval of ten to twelve days or longer is allowed to elapse before another dose is administered, the animal on the second injection may undergo severe constitutional disturbance with collapse that may be fatal. If however, the second dose of serum is given before the tenth day, there is no anaphylactic shock, and furthermore, Bursreda has found that if a small dose of the serum is given per rectum ten hours before or subcutaneously five hours before the second injection, it produces a condition of antianaphylaxis in an otherwise susceptible animal. There are other protein poisons such as those formed in the poison glands of snakes and scorpions or the protein of certain grass pollens. The protein of grass pollen cannot be regarded as a toxic substance in itself, since most persons are not affected by moderate doses, but a few however, show an abnormal sensitiveness to pollen and it causes in such subjects, hay fever or hay asthma. I have a patient who shows an acute sensitiveness to minute quantities of egg albumin. All such conditions have an affinity with the acquired sensitiveness to foreign proteins known as anaphylaxis. This anaphylaxis is presented with great regularity in the guinea pig. The symptoms presented in anaphylaxis are, circulatory collapse, vomiting, dyspnoea and prolonged prostration. Several fatal cases
have been recorded and even with hypodermic injection, severe symptoms coming on within an hour or two of injection, are seen in a certain number of these cases, and some of the worst cases recorded have occurred in cases of prophylactic injection into healthy persons exposed to infection. Children are not so liable to anaphylaxis as adults.

Serum Rashes. This is another type of toxic phenomena produced by the use of serums. In a certain proportion of patients (usually about 25%) an injection of serum is followed after an interval of ten to twelve days, by a reaction which usually takes the form of an urticaria and this is sometimes complicated by joint pains and facial oedema. The rash is often accompanied by pyrexia and the joints affected are generally the wrists, elbows, knees and ankles. Suppuration of a joint is very rare but I believe Goodall has met with it. These symptoms may be unpleasant but are rarely serious. I have seen cases of urticaria following the use of serum and also a few cases of circinate erythema, and some authorities believe that in diphtheria a smart serum reaction especially when accompanied by pyrexia, is often of great benefit to a patient with feeble pulse and subnormal temperature. The serum rash and serum sickness may follow one injection only, but will follow more rapidly when a second injection is made. The erythematous rash is usually seen in the more severe reactions.
Another fact observed is that those cases which display enlarged tonsils, adenoids, etc., show a greater tendency to "serum disease" than to simple rash. All the eruptions display a marked characteristic feature in their fleeting and evanescent nature. A patient may be covered with urticaria and in an hour or so only show a few isolated patches; the lapse of an hour or two may find him covered with the rash again. The rash not infrequently involves the respiratory mucus membrane and may cause a croupy cough.

Treatment. An ointment of menthol and paraffin will relieve the itching and calcium chloride has been recommended after the injection of serum. Some authorities hold there is less liability to rash after the use of concentrated sera but some believe that the serum of some horses is more provocative of serum sickness than is that of others.

Pathological changes found in cases of death after diptheria.

Mallory found that the vagus nerve in fatal cases of diptheria always showed some evidence of degenerative changes; also marked fatty degenerative changes have been found in the medulla. Mallory also found fat in the muscle fibres of the heart, hyaline degeneration and evidence of interstitial myocarditis. He has also found diffuse fatty degeneration in the white substance and nerve fibres of the central nervous system. Some authors have advanced the theory that many of the symptoms met with in severe cases of diptheria are due to suprarenal insufficiency and pathological changes in
The supramaxillary glands have been found in fatal cases of diphtheria such as atrophy of the cellular elements causing a complete loss of function.
SUMMARY.

Medical men should have every facility offered to them by the Local Health Authority for obtaining a bacteriological diagnosis of material from suspected cases, and an unlimited supply of antitoxin should be obtained gratis by applying to the Public Health Offices, and the medical attendant should answer the following questions at the termination of the illness:

Name of Patient,
Age,
If verified by bacteriology,
Amount of serum used,
On which day or days of illness,
Result,
Sequelae if any.

Of course a case of diptheria should be notified at once to the Medical Officer - but in dealing with the spread of diptheria the great difficulty is how to deal with infected healthy contacts. These people show no signs of ill health, but at the same time they are carrying virulent bacilli - in the case of children they ought not to be allowed to return to school until they have been certified to be free from Diptheria Bacilli. Schools play an important part in the spread of the disease, and when day schools are closed during an epidemic the order should also include Sunday Schools. - I have already
referred to one epidemic in which I thought it advisable to destroy all the books used by the scholars. It is of great importance to isolate healthy infected contacts if possible, and it has been proved that one negative culture is not sufficient evidence of the disappearance of the bacilli from the throats of infected persons. - In three instances at least in my practice I have been convinced of the spread of diphtheria from healthy contacts - and cases of infection from patients long after they have recovered have frequently been recorded. Personal infection in my experience is the most important factor in the spread of diphtheria. I have had no experience of post-Scarlatinal Diphtheria - although I have witnessed numerous epidemics of Scarlet Fever in Briton-ferry, and as far as I know it is not usually met with in private practice, but it is of frequent occurrence in Fever Hospitals, and it is undoubtedly due to the introduction of unrecognised cases of diphtheria into Scarlet Fever wards. - But I have under my care at present a case of post-influenzal diphtheria in a girl aged nine years. - She was taken ill with Influenza and on the ninth day of the illness she had typical diphtheritic membrane on both tonsils and on the uvula, after one injection of 4,000 units, the membrane disappeared, there was a severe epidemic of Influenza raging at the time. In October 1918 I was called to see an unusual case - a girl aged eight years had suffered for seven months from an
extensive vesicular eruption on the skin over the whole of the body - and the complaint had defied all treatment. - I saw the child every day and I found there appeared on various parts of the body a fresh crop of vesicles every day. - These vesicles were scattered over the back especially across the shoulders, over the abdomen and over both arms and legs, also a few small vesicles appeared on the face - these vesicles were filled with clear serum - then became crusted - dried and formed a scab, almost impetiginoid in appearance, but the most characteristic point about it was the fresh crop of vesicles every day. The disease was not pemphigus and the usual treatment for the latter had not the slightest effect on it, no local application was of any use, and the complaint defied all internal treatment. - The vagina looked raw and inflamed with a slight exudation, and according to the evidence of the mother this condition had appeared at the commencement of the complaint. - As I was dealing with two cases of diphtheria at the time I began to question in my own mind whether I was dealing with a case of diphtherial infection of the skin - so I sent two slides up to London with a specimen of the clear fluid from two vesicles - The report said - There were certainly some diphtheroid bacilli present. - The next day I injected 4,000 units of serum, and in my opinion apart from the bacteriological report - the injection determined the
diagnosis of the complaint - for the effect was truly surprising. The scabs at once healed up, and the vesicles ceased to appear - I may say I took no swabs from the throat - My locum Dr O'Connor of London saw this case at the end of September 1918. On looking up the literature of diptheria I find a similar case was reported in the Lancet Jan. 4th, 1908 by Dr A. R. Slater - I wrote to the Lancet for a reprint of this paper - but they replied they were unable to do it - so I have not seen the article - I have no doubt this was a case of chronic diptheria of the skin or Chronic Diptheritic Dermatitis.

Some individuals prove more susceptible to diptheria than others - and I have been long enough in Briton-Ferry to have seen diptheria in the second generation - I know one family here where four of the children have been attacked by diptheria at different periods.

Mortality. Diptheria attacks children under the age of ten, and in my own cases the most fatal age period was under 5 years. I have seen a large number of cases of diptheria but I have only kept careful records of the 50 which are under review in this Thesis. In addition to these I had another 5 cases of the disease this winter with no deaths. - The 50 cases were composed of 32 Males and 18 Females, there were 8 fatal cases which makes a mortality of 16%, five of the cases were ill for an indefinite period before receiving treatment.
The causes of death in the above series of cases were:

- Cardiac paralysis (per se)  2
- Toxaemia                  4
- Syncope after Tracheotomy 1
- Broncho Pneumonia         1

As mentioned before, I have not performed tracheotomy since the introduction of Antitoxin - but in the two years previous to the discovery of Antitoxin I performed this operation five times - and I know at least of these cases are living in Briton-Ferry at present. In looking up the Mortality among my cases I find no deaths recorded among my sporadic cases. The deaths have occurred during epidemics and not during the decline - and in my opinion there is a definite change in the character of the organism during an epidemic, for instance there is no doubt the bacillus is more infective during an epidemic than in sporadic outbursts. - Before the introduction of antitoxin the mortality among children under 5 years of age was 50 per cent - now it is about 13. It is said to attack more females than males - This is not my experience. - There is no doubt, hospital treatment irrespective of any specific treatment gives the patient a better chance of recovery, but even with home treatment the use of antitoxin has completely altered the chances of recovery of a patient, especially if the serum is used on the first day.
But the opponents of serum therapy contend that the disease is becoming milder, but this is not true as regards this place for the five cases I have seen this winter were as severe as any cases I had witnessed before the use of antitoxin, and again the mortality among those who do not receive antitoxin is still as high as ever, and there is no doubt diptheria when not treated is a very fatal disease. In my experience the most dangerous stage of faucial diptheria is the port febrile, and after the disappearance of the membrane the patient should be kept lying down for many weeks quite apart from the superintention of paralysis - for in cases that have appeared to be benign, serious symptoms of cardiac failure may suddenly arise - but often these symptoms may come on gradually - thus particular attention should always be paid to the state of the pulse. The more persistent the exudation, the worse the case, and early paralysis of the palate is a bad sign, especially if it is associated with an extreme pallor of the face - Lobular pneumonia is a grave complication. The initial vomiting of diptheria has rarely any prognostic significance, but it is a leading issue in cases of late sickness, because this is loss of both food and water - rest is disturbed and physical exhaustion is induced. I have often noticed a sudden pallor, and a quickening of the pulse and some irregularity when a patient is allowed to sit up due to
careless nursing - for the direct treatment of cardiac weakness, there is no doubt alcohol is very useful - and I have also found benefit from the injection of adrenalin Solution 4 - 8 min to 1,000.

Exertion should be prohibited for some weeks after the patient has been allowed to get up.

The effect of the antitoxin is well brought out in the outbreak of diptheria in Colchester in 1901 - Prior to July 16th antitoxin was not given as a routine treatment, and reliance was placed on antiseptic sprays to destroy the bacilli - after July 16 - antitoxin was given to every case. During the first period the case mortality was 28 per cent, during the second period the case mortality was 5.6 per cent. - The introduction of the new treatment was followed by a succession of 60 cases without a single death.
The reason why my death rate is high is because it includes the deaths before 1895. In my last 14 cases I have had one death, and this was no doubt due to the serum being given too late. Dosage has an important influence on case mortality. Of course it is known how much antitoxin is required to neutralize a given amount of toxin; this is not done in any given case, but conclusions are drawn from experience and clinical studies. It is better to administer too much antitoxin than too little, thus the dosage should be large. In cases of exceptional severity and where the injection is given late I have given 8,000 units and I have repeated this dose in 10 hours. Time of administration is very important but no matter how late a case is seen an injection should be given. Cases treated very early give the best results.

This is well shown by the following table prepared by the New York Health Department, 1902 - 4.

<table>
<thead>
<tr>
<th>Day</th>
<th>No. Cases</th>
<th>Case Fatality</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>623</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>1639</td>
<td>53</td>
<td>3.3</td>
</tr>
<tr>
<td>3 ≤ 4</td>
<td>1871</td>
<td>127</td>
<td>6.7</td>
</tr>
<tr>
<td>5 ≤ over.</td>
<td>455</td>
<td>82</td>
<td>18.0</td>
</tr>
</tbody>
</table>

The reduction in the mortality rate since the introduction of antitoxin was comparatively small in the first three years of its use, but this is explained by the fact that sufficiently large doses of antitoxin were not used at first and that the serum used later was more efficient.

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